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EDITORIAL

"TIME STAYS—WE GO."

Still another wisp of man-defined time dissolves in the vastness of eternity as 1923 speeds out, its puny program ended. And another worn-out calendar goes the road of worthless things as in its place is hung the glossy herald that counts the time for 1924.

Already the new calendar carries vivid marks of human hopes, for certain dates thereon are even now discounted. Already the future is mortgaged and folks for whom tomorrow is but a fragile promise get comfort from the thought that these red-letter days, their special days of great events, are bound to come.

Here is a mark across that day in June, which speaks for celebration—that rare day in June, when together they walked the long rose aisle—and how they have gone it together since—roses with the thorns and thorns for all the roses—yet the red blotch upon their calendar is sweet promise that not forgotten shall be that merry day.

Here are marks that may mean birthdays—others, days of special import—then the later days of Summer, when work is left behind and the time of rest is come.

"How futile!" speaks the pessimist.

"How human!" answers the optimist.

"O Wind, if Winter comes, can Spring be far behind?" That is the song of the optimist, who ever knows that all the days, red-letter and unlettered days, are bound to come.

How human—how beautifully, optimistically human indeed, is this bartering with the unborn days—this dickering in flimsy futures.

Yet despite the hopes, the longings and the promises the new calendar is only symbol for the hooded figure—the changeless

hooded figure that stays when years and decades and centuries pass on in scurrying procession.

They are gone, *we* are going, *others* will also vanish—only the hooded figure stays—with bowed head standing and watching the parade of people go by.

"Time goes—you say?
Ah! no!
Alas, Time stays;
We go."

On with our voyage, then, and as we go let us renew our cordial pledges. Let us be thankful, as we hurry on, that Time, the Immutable, suffers us to hope and to remember—to fashion dreams and fill our hearts with memories.

. . . . .

The JOURNAL again extends to its world-wide circle of reading friends its earnest felicitatons. To the contributors whose only remuneration has been the privilege of its pages it offers its hearty thanks and bids them again to its forum. Approaching its centenary, it aims to keep its standards high, its ethics unimpeachable—it aims to keep as virile and as worthy in service as the great Institution that sponsors and supports it.

IVOR GRIFFITH.

THE "POISON RUM" PROBLEM.

Deaths from "alcoholism" were not infrequently reported by coroners and health authorities long before methanol or any other intentional or accidental addition of specifically toxic substances was probable or even possible. In these cases, it was assumed that the fatal result was due mainly to the characteristic ingredient of fermented beverages, the ethyl hydroxide. It was taught, however, in medical and pharmaceutical schools and generally accepted, that newly-distilled spirit contained a notable amount of the higher alcohols, especially the amyl hydroxides; that these were highly toxic and responsible for some deleterious effects, and that storage brought about an oxidation of them to harmless esters of pleasant flavor. A general rule was made that to be fit for medicinal use, whiskey must be at least two years old. Fifteen years ago Cramp-

ton and Tolman (*J. A. C. S.*, 1908, 30, 98) reported the results of extensive and careful tests of the effects of storage on spirits. They found that no appreciable change of the higher alcohols (commonly grouped under the title "fusel oil") occurred even after eight years. In fact, as the ethyl hydroxide evaporated a little more than the water, the percentage of fusel oil to it was slightly higher at the end of the storage period. They also found that the aroma and color acquired was due to the charred staves of the cask, and that the same spirit kept in glass bottles underwent no change in either respect. They made careful determinations of accessory products, acids, esters, furfural, acetaldehyde and fusel oils, and found small amounts of such substances in most of the samples.

In the last two years the scene has changed materially. The sale of liquors containing more than a very small amount of ethyl hydroxide is unlawful throughout the United States and the places subject to its jurisdiction, and many forms of violation of the law have been brought to public notice. The principal methods have been so far the secret distillation of a fermented mash and the purification of denatured alcohol, now easily available at a low price. It is an interesting evidence of the insincerity of the common appeal for such a modification of the law as will permit the sale of "light wines and beers," to use the familiar shibboleth, that almost all the seizures and prosecutions for violation of the prohibition laws are for the manufacture and sale of highly alcoholic liquors.

Accurate data on the composition of the commercial liquors, both those manufactured in pre-prohibition days and those now obtainable, seems to be scanty. Sensational reports of deaths from "poison rum" are, of course, to be read in the newspapers, to which such data are acceptable, but the earnest inquirer will ask, "Where are the analyses?" In Philadelphia, it is stated, on the authority of the Coroner, there have been in the past year a great many deaths from such liquors, but the crucial test, an analysis of the liquor used by the victim, is not seemingly in evidence. If known to the Coroner and other authorities, these data should be made public promptly, not buried in some annual report that no one reads but the writer, compositor and proofreader.

Recently some specific data of a comprehensive nature and from trustworthy sources have been published. Doran and Beyer, of the United States Internal Revenue Department, presented at the meeting of the American Public Health Association a paper

embodying the results of analyses of about 75,000 strongly alcoholic liquors concerning which criminal proceedings had been undertaken. The paper was published in the *Amer. Jour. Pub. Health,* and reprinted in the AMERICAN JOURNAL OF PHARMACY (1923, *95,* 920). Attention is first called by the authors to the difference in the manufacture of the so-called "moonshine" whiskey, in the mountain regions of Kentucky and West Virginia, and the methods now much in vogue in the illicit distillations in the country at large for the purpose of supplying the bootleggers. In the original moonshine operation the spirit chosen was the middle run of the still, the early portions and the undistilled remainder were either rejected or mixed with other mash and redistilled. It is claimed that by this method a safer distillate is obtained. As the conditions under which illicit distillation takes place lead to more careless procedures, the dominant motives being rapid operation and large yield, a spirit is produced that is much inferior in all ways to even the "mountain dew" that has been so long the object of raids by the Internal Revenue Bureau.

What now are the facts set forth by the authors of the paper? They assert that in the light of Crampton and Tolman's report, they cannot ascribe any deleterious actions to the acids, esters, furfural and higher alcohols found in the samples of illicit spirit, for the amounts of these accessories are close to those found in spirits made legally and under the best conditions. One accessory, acetaldehyde, was found in notably greater proportions, as to maximum, minimum and average, than in Crampton and Tolman's analyses. This excess of acetaldehyde is naturally charged with the alleged poisonous action of the spirit. The clinical histories of the poison cases are not set forth, but this is not the duty of the analysts. It is to be regretted, however, that the analytic data are not accompanied by a summary of the physiologic and pathologic effects. The largest proportion of acetaldehyde found by Crampton and Tolman was fifteen parts per 100,000; the largest found by Doran and Beyer was 100 parts in the same amount. The contrast is imposing, but a little thought will show that the inference as to the effect of such impurity may not be sound. One hundred parts per 100,000 is one part per 1000, approximately 1 cc. per liter, expressed in familiar measures, half a thimbleful to the quart. Is it sound pharmacology or physiology to assume that a substance such as acetaldehyde, which is present in almost all alcoholic beverages, is so poisonous that the amount

usually taken by even the worst type of addict will produce promptly very serious and even fatal results? Doran and Beyer give some references to animal experimentation, but the most direct of these seems not to bear out their judgment. A German reference states that from 1 to 2 cc. were administered to rabbits, which were also subjected to prolonged inhalation of the vapor. Slow arteriosclerosis was the principal result. Inhalation experiments are, of course, of no value in testing out the effects of the consumption of the substance by the mouth. The late Professor Holland's "Chemistry" is also quoted, but this is a secondary authority, and if the full paragraph is given it will be seen that a statement is made which cannot now be accepted.

That continued use of strong drink containing notable amounts of acetaldehyde may produce disease, may be conceded, but it is likewise true that continued use of strong drink containing nothing but ethyl hydroxide will give rise to disease. The lack of specific and detailed clinical histories as to what occurs in the cases of death from so-called "poison rum" renders positive judgment impossible, but the language commonly used in the newspapers and seemingly implied in the paper by Doran and Beyer suggests that the effects are prompt and severe after comparatively moderate amounts of the liquor have been taken. If such is the history, it is impossible to ascribe the effects to the presence of acetaldehyde in proportion of about a thimbleful to the quart which is the highest proportion that Doran and Beyer found. In all cases in which sudden severe or fatal illness results after the drinking of strong drinks the *corpus delecti* does not seem to be acetaldehyde in view of the data at present at hand both as to its effects or as to the amount in which it may occur in the given article. No comparison can be established between the effect of 1 cc. on a rabbit or prolonged inhalation of the vapor, and the conditions under which moonshine or other illicit spirit is used.

It should be noted that the highest proportion of acetaldehyde found by Doran and Beyer (one part per 1000) was in a sample that contained 77 per cent. of alcohol by volume. Such a spirit would not be drunk by any one in undiluted form, so that the amount of aldehyde ingested would be much less than 1 cc. to the liter.

HENRY LEFFMANN.

ORIGINAL ARTICLES

LIGATURES AND SUTURES.

By Dr. Fred B. Kilmer, Ph. M.; G. S. Mathey, Ph. G., Ch. G., B. C., and H. J. Dobbs.

This is the fourth and last of a series of papers discussing the subject of Ligatures and Sutures from a pharmaceutical standpoint. While in many respects elementary and incomplete, it is hoped that its publication may assist the pharmacist in handling this class of material.

THE SELECTION OF THE LIGATURE AND SUTURE.

While it is not within the province of the pharmacist to even attempt to instruct the surgeon as to the kind and size of material which he shall use, he should, however, be sufficiently informed on the subject to discuss it intelligently, and he may often be able to adroitly assist the surgeon in his selection.

The following notes have been compiled from many years' contact and discussions with surgeons, thus gaining their practical experience in the operating room.

Section of Muscle, fourteen days. Few remaining remnants (2) imbedded in dense mass of lymphocytes (1).

Section of Muscle, seven days. Ligature (2) opened into strands and extensively infiltrated. Remnants of the strand have become obliterated.

The Size to be Chosen.

The small size suture is more quickly absorbed under the same conditions than a larger suture. It has less bulk, and as a result the tissue fluids can creep in more readily and soften it.

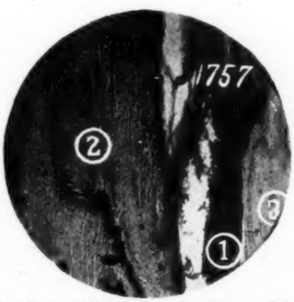
The danger in using a small-sized suture, under ordinary circumstances, lies in the fact that it might soften too soon, *i. e.*, lose

its function as a suture before the wound had completely healed, and as a result the wound may spread open or "gap."

If possible, however, it would be an advantage to use a small suture because it is less of an irritant to the tissues than a larger suture, and therefore the tissues are not taxed in trying to take care of it.

Strictly speaking, all ligatures are "foreign bodies," but, of course, a smaller suture is less of a foreign body than a larger one. This is particularly true of the knot, which is about eight times as bulky as the suture itself, and as it lies in a place where there is less secretion than at any other point along the suture, (*i. e.,* in an "unabraded surface"), the knot is the last thing to become absorbed, and is the greatest source of trouble.

Another point in favor of the use of small sizes is the fact that the surgeon is less likely to tie too tightly than he is with a heavier size, and as a result he is less apt to interfere with the circulation of the blood; in other words, with the smaller suture there is not as much danger of necrosis from strangulation, and the surgeon is enabled to make "nicer approximation."



Section of Muscle, six days. Ligature (2) infiltrated with lymphocytes. Absorption indicated by frayed-out appearance.

Section of Muscle, five days. Ligature (2) surrounded by lymphocytes (1).

Chromic or hardened catgut enables the surgeon to use small sizes of sutures without running the risk of their absorbing prematurely. For example, No. 1 medium hard catgut is being used with the greatest safety in layer suturing of the abdominal wall, but this same size of plain catgut might absorb too quickly and cause the wound to gap. Chromic catgut, therefore, protects the surgeon in the use of small sizes.

This means that the tax on the absorptive powers of the tissue is minimized (especially at the knot), and the danger of "for-

eign body irritation" lessened. In addition, there is less culture medium offered to the bacteria which are bound to be in the tissues to a greater or lesser extent.

Not only is there the danger of producing a clumsy, bulky knot with a heavy size, but also there is the danger of not getting a compact enough knot, so that when it becomes moist it may loosen, and even become untied, which, of course, would be a very serious matter. In the case of the ligature, it might mean "secondary hemorrhage," and in the case of the suture, it might mean the gaping of a wound or a hernia.

The following table shows the sizes and kinds of suture material which many surgeons have found to give the most satisfactory results in the different tissues:

Striated Muscle	No. 1 or 2 medium hard
Fascia	No. 0 or 1 medium hard
Skin (through and through)	No. 0 or 1 medium hard or plain, silkworm gut or horsehair
Skin (subcutaneously)	No. 00 extra hard or No. 0 medium hard
Peritoneum (alone)	No. 00 or 0 medium hard
Peritoneum (through and through)	No. 1 or 2 extra hard
Cervix	No. 2 extra hard
Vagina	No. 2 extra hard
Kidney	No. 2 extra hard
Stomach, Intestines and Glandular Tissue	No. 0 or 1 extra hard, re-enforced by silk

As far as the skin is concerned, most surgeons do not recommend the use of catgut at all, on account of the fact that the skin can never be made entirely sterile, and as a result catgut might become infected and act as a culture medium for the organisms present. Then, again, there is danger of its absorbing too rapidly, because there are more lymphatics in some portions of the skin than in other portions. For these reasons, silkworm gut, silk or horsehair is more desirable.

But catgut can be used successfully in the skin if it is put in "subcuticularly," *i. e.,* underneath (or through) the cuticle of the skin, so as not to come in contact with the "sweat glands" or "hair follicles." Under such conditions there is little, if any, danger of its becoming infected. The material which has been found to give the best results in this way is the No. 0 medium hard.

The Surgeon's Point of View.

The extent to which the pharmacist will be able to help the surgeon in the selection of suitable materials depends in some measure upon his knowledge of the rudiments of anatomy and physiology, and his comprehension of the subject from the surgeon's point of view.

Let us consider an abdominal operation: When the surgeon makes his incision, he first cuts the skin, which is a covering constructed in three layers, the outer, or "epidermis," then the "corium," or true skin, and lastly the "subcutaneous connective tissue." In this connection it must be remembered that it is practically impossible to sterilize the skin, no matter how much it is scrubbed or painted with antiseptic solutions, and for this reason absorbable materials, such as catgut, are regarded with disfavor for suturing the outer layer, although sometimes catgut is used "subcuticularly" or under the cuticle. Silk is more usually preferred, but this is only second to silkworm gut and special skin sutures, which are generally regarded as ideal, since they are smooth and easily removed.

Section of Peritoneum, seven days. Ligature (2) not very much acted upon, but surrounded by a deposit of lymphocytes (1).

Section of Peritoneum, nine days. Ligature (2) has not opened into strands, but is surrounded by a dense mass of cells (1). Newly formed tissue (3).

Beneath the skin lies a layer of fat, varying in thickness with the location and individual. Fat is very easily infected, and equally as easily "necrosed," if a stitch happens to be tied too tightly.

Under the fat is found a layer known as the "superficial fascia," serving as a covering to the muscles beneath it.

From a suturing standpoint the relation of the muscles to the fascia is very intimate, in fact, many surgeons make it a practice to suture the muscles with the same material with which the fascia

is sutured, so that from the foregoing it will be gathered that what can be used in the muscle can also be used in the fascia.

In some parts of the abdomen there exists another fascia known as the "deep fascia," which it is frequently found difficult to separate from the peritoneum lying beneath the muscles, and consequently little or no attempt is made to suture them separately.

Inside the peritoneum lies the abdominal organs.

There are many ways of suturing, two of which should be remembered, because, as will be found later, the material used in one instance should differ from the material employed in the other.

The technic of the tier plan of suturing embodies, as its name implies, the sewing of each layer separately, or in tiers, while the through-and-through method consists in passing the suture through all layers. The through-and-through suture is seldom practiced outside of extreme cases of emergency.

Now, let us refresh our memories: In a previous section dealing with the subject of chromicization it was pointed out that catgut was hardened in relation to the period of time it was required to resist absorption in ordinary striated muscle tissue, and furthermore it was shown that serous and mucous membranes absorbed catgut practically four times as rapidly.

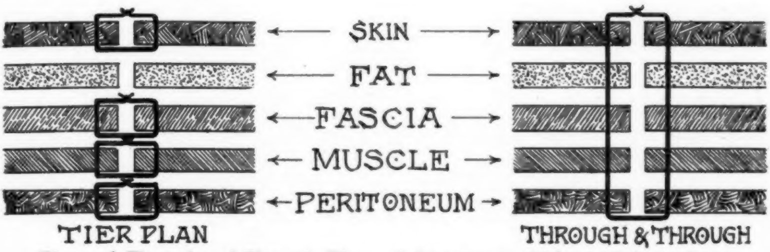
Under this latter classification, then, must be placed the peritoneum, but while this membrane digests catgut so rapidly, the union of the cut edges is equally as rapid; in fact repair is effected within twelve to twenty-four hours, so that by the use of a medium-hard (twenty-day) chromic catgut one can rely upon its integrity for approximately four or five days, thus securing a fair margin of safety.

In the muscle and likewise in the fascia, medium-hard (twenty-day) chromic catgut suggests itself, affording a resistance period of well over the ten days allowed for primary union.

Attention is now focussed on the fact that in both the peritoneum and muscle, medium-hard (twenty-day) chromic catgut has been suggested for use when the tissues involved are sutured under the tier plan; if, however, necessity demanded a through-and-through suture it would not be wise to recommend the medium-hard (twenty-day) catgut for the reason that at the expiration of four or five days the peritoneum will have digested that portion of the catgut passing through it, thus removing the tension which should hold in apposition the muscle edges for ten days.

To meet such conditions extra-hard (forty-day) chromic catgut may be used with impunity.

In suturing the cervix-uteri, vagina, rectum, kidney, stomach and intestines the extra-hard gut is generally used, re-enforced with stay sutures of silk, or because of the fact that there is such an abundance of ferments or "enzymes" in these parts that even the extra-hard gut is likely to break down too soon. Although a great many surgeons are using catgut safely, the more conservative men look upon it as a rather risky thing, and inasmuch as the non-absorbable sutures, like silk and silkworm gut, do not seem to cause any trouble in these glandular tissues, there is no danger in their use, but there may be danger in the use of even the extra-hard chromic catgut.



Tier and Through-and-Through Plans of Suturing in Abdominal Operations.

The consensus of surgical opinion, therefore, is that the only tissues in which catgut might not be as safe as silk, are the stomach and intestines; and then again, of course, in the skin, on account of the danger of its becoming infected.

While the extra-hard gut is safe enough in the perineum in "secondary repair," it is not considered safe enough in "immediate repair." Immediate repair of the perineum is that which is made immediately after childbirth. For the following week or ten days there is a discharge of fluid known as "lochia," and many physicians prefer not to suture a lacerated perineum until the flow of this discharge and the swelling of the tissues have subsided, that is, not for about a week or even two or three weeks after the delivery of the infant. This is called "secondary repair," and the significance lies in the fact that in secondary repair there is no lochia, while in immediate repair there is, and although extra-hard gut holds ten or twelve days in secondary repair, it is not supposed to hold anywhere near that length of time when the lochia comes in contact with it.

For use in obstetrics special chromicized catgut called "obstetrical catgut suture," is prepared to hold in spite of the lochia for ten to twelve days.

The pharmacist, through a study of the adaptability of the various forms of ligatures and sutures to particular needs, can gain the confidence of his medical patrons by being able to assist them in making their selection of ligature and suture material.

Ligatures and Sutures in the Operating Room.

After the surgeon has selected the required kind and size of suture material, the pharmacist can still be of service in its progress through the operating room into the tissues of the patient.

Ligatures and sutures are now supplied in two principal forms: tubes and envelopes.

The tube form is the one most largely used. In this form the ligature is sterilized and covered with a preserving liquid, such as alcohol, chloroform, etc. The tube is then flame sealed. A file mark carried around the tube permits easy breaking open at that point.

A demand has been created for two quite distinct kinds of suture material, known as "boilable" and "nonboilable." This distinction is important, and should be strongly impressed upon every person who handles the material. The terms refer to the manner of disinfecting the outside of the tube. The material inside the tube is intended to be sterile in either case.

The disinfection of the exterior of the tube bears no relation to the sterilization of the contents of the tube.

With the "boilable" tubes the outside of the tube may be sterilized by boiling in water or placing the tube in the steam sterilizer with instruments and dressings.

Tubes labeled "nonboilable" cannot be boiled or subjected to the steam sterilizing process.

The difference lies largely in the preserving fluid in the tube. In the "boilable" tubes this fluid is of such a nature that the tube and its contents are not injured by the heat. In the "nonboilable" tubes the fluid usually carries a small percentage of moisture to keep the ligature soft; hence, boiling or steam sterilization would ruin it.

"Boilable" sutures are the more hard and wiry, "nonboilable" are the more pliable.

Boiling the Tubes

The usual method of procedure is as follows:

The tubes to be used for the operation are wrapped in a piece of gauze holding all of the tubes necessary for the operation. The gauze package is then placed in the instrument sterilizer for the usual thirty minutes. The gauze prevents the instruments from striking against the tubes and possibly breaking them, and should always be used. If broken while heating they are apt to explode, by reason of the explosive nature of the fluid in the tubes being under pressure from the heat.

When taken from the sterilizer, the tubes are allowed to cool, after which they are broken in sterile gauze, and the suture removed. If required by the surgeon, it may be dipped in sterile water in a sterile dish and handed to the operator.

Opening the Tube.

In opening the tube care should be taken to break it at the designated point, so as to avoid ragged glass edges which are apt to cut or abrade the catgut and thus weaken it. Even if the tube is properly broken, without injury to its contents, another danger exists in the way the loops of catgut are straightened out previous to use. If these are gently unwound without kinking, no harm will result. But if the ends are seized and the strand forcibly and quickly pulled out straight without regard to the loops, tiny twists are sure to occur at several points, which abrade the catgut and lower its tensile strength essentially.

A strand of catgut should not be immersed in water for over five minutes. It should then be laid in folds of gauze until wanted for use.

A better method than immersion in water for softening the catgut in the operating room, is to lay the strands between folds of a sterilized towel or gauze which has been made damp. The catgut will absorb sufficient water to become pliable.

To sterilize the outside of the glass tube containing catgut of the "nonboilable" variety, requires a wholly different process from that which is "boilable." The usual method is to wash the tube with soap and water and immerse in a disinfecting fluid. Herein difficulties arise. The tubes are apt to be coated with grease, dust and dirt, carrying organisms. Many watery fluids will not penetrate the coating and destroy the bacteria.

One of the difficulties surrounding the use of antiseptic solutions for disinfecting the exterior of ligature tubes is that the tubes float in the solution and the ends protrude above the liquid and, consequently, are not sterilized.

The tubes must be weighted down by means of a perforated disk heavy enough to hold them under the solution.

The following solutions have been found to work out satisfactorily for disinfection of the exterior of the tube:

Formulæ for Disinfecting Exterior of Ligature Tubes.

HARRINGTON'S SOLUTION:

Water, ten fluid ounces; alcohol, twenty fluid ounces; hydrochloric acid, two fluid ounces; mercuric chloride, twelve grams.

Used full strength it will disinfect in ten minutes exposure.

MERCURY OXYCYANIDE SOLUTION:

One part mercury oxycyanide to 1000 water.

Full strength will disinfect in ten minutes.

MERCURIC IODID SOLUTION:

One gram mercuric iodid dissolved in 5 cc. of a 20 per cent. solution of potassium iodid, adding distilled water to 500 cc.

Full strength will disinfect in ten minutes.

POTASSIUM BICHROMATE SOLUTION:

Potassium bichromate, ten grams dissolved in a 10 per cent. solution (by volume) of sulphuric acid, C. P.

Diluted 10-100 disinfects in twenty minutes.

HYDROCHLORIC ACID SOLUTION:

Hydrochloric acid, C. P.

Diluted 15-100 disinfects in ten minutes.

FORMALIN SOLUTION:

Thirty parts of formalin to seventy parts water by volume.

The envelope form of package for sutures is prepared as follows:

The ligatures are first wrapped in one piece of heavy manila paper and then in a second piece. The sterilization is done after sealing in two papers or envelopes, and the ligature is not handled thereafter until used by the surgeon. These double-wrapped sutures are then placed in the outer protective envelope.

In handling enveloped ligatures in the operating room, the procedure is usually as follows:

Nonsterilized hands open the papers, touching only one end of the inner paper. The same nonsterilized hand holds the same end of the inner paper while a sterile hand cuts, with sterile scissors, the untouched end of the inner and sterile paper. Following this a sterile hand with sterile forceps removes the ligature from the cut end of the inner sterile paper.

If the operating room is free from ether vapors, the cut end of the inner paper may be passed through the flame of an alcohol lamp before the ligature is withdrawn. The sterilization of the container is made perfect by burning the end of the paper, and by this means also the necessity of careful handling of the papers, as previously described, is done away with.

Softening Catgut.

After the catgut has been removed from its container, in the operating room, many surgeons immerse the strand in water or watery solutions (physiological salt solutions, etc.), to increase its pliability. In this procedure complications may arise, especially when those handling the material are not fully aware of its nature. Here the pharmacist can help.

Catgut is softened and rendered pliable when immersed in water, but it can be injured, and sometimes greatly injured, by too long an immersion.

In some operating rooms it is the practice to immerse the catgut at the beginning of the operation, and allow it to remain until required for use—an indefinite period, which may vary from a few minutes to an hour.

From a series of experiments in our laboratory we have reached the following conclusions:

Upon immersing catgut in water the first action is that of swelling and softening. The cord becomes pliable and slippery. On continued action there is a lessening of the tensile strength. The smaller the size of the strand the more marked the action of the water.

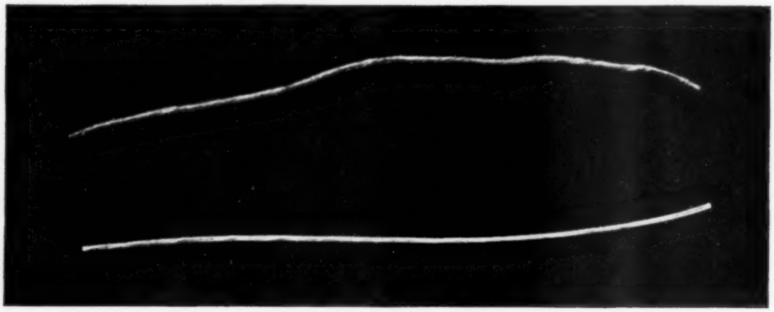
The temperature of the water is important. The action is slower in cold than in warm water. The use of hot water is dangerous. The water should not be above room temperature.

There should be established a maximum and minimum time of

immersion for each size. Below the maximum time the strand is not sufficiently softened; above the maximum time the catgut is softened too much, and its tensile strength impaired.

A method used in many hospitals for softening the strands, is that of placing the strand between the folds of a moist towel. This is much more safe and in all ways preferable to the immersion method.

The process is simple: A sterile towel is dipped in cold sterile water, or a 1-1000 solution of mercury bichloride, and wrung out by hand. The strands of catgut are laid between the folds of the towel. In this method the softening is slower, more uniform, and there is less danger of carrying the softening too far.



The action of water on Catgut. The two pieces are from the same strand. The larger-sized strand has taken up water and swollen.

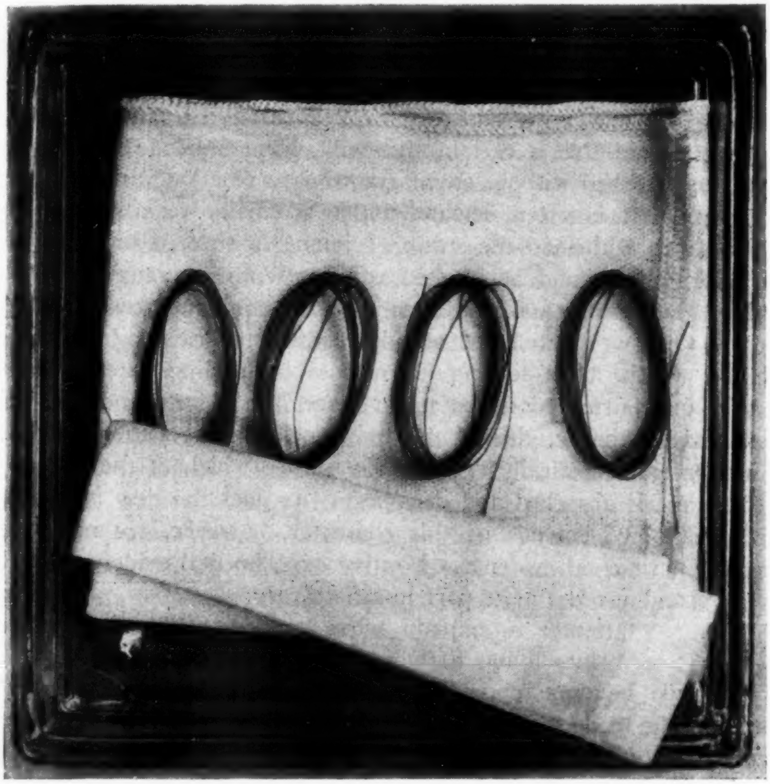
A third method of softening catgut prior to use is immersion in 60 per cent. alcohol. In this method the action of the fluid is slower and not destructive. It is by far a more satisfactory procedure than either of the foregoing.

We have, as a guide, established a minimum and maximum time for the immersion of catgut by each of the methods described, as follows:

CATGUT IMMERSION.

Minimum Time in Minutes.			
Size	*0*	*1*	*2*
Immersion in water,	½	3	4
Between folds of moist towel,	3	10	15
Immersion in 60 per cent. alcohol,	8	15	25
Maximum Time in Minutes.			
Immersion in water,	3	6	8
Between folds of moist towel,	10	40	60
Immersion in 60 per cent. alcohol,	30	50	80

Water should be that which has been sterilized, and should be used at room temperature.



Method of softening strands of Catgut by placing between folds of wet towels.

Catgut in the Tissues.

Why should a strand of catgut imbedded by the surgeon in the tissue concern the pharmacist?

Catgut is an important agent in wound healing; practically it comes under the accepted definition of the word "drug." The action of catgut in the tissues involves problems in what might be termed pharmacodynamics or pharmacology.

A knowledge of suture material is incomplete without some knowledge of the fate of the material after it becomes implanted in the tissues of the patient.

This is a most difficult subject of which comparatively little

is known, the best of surgeons have very obscure ideas upon the matter.

The solution of problems involved requires the joint action of the pharmacist and the surgeon.

The views of surgeons are greatly varied, and there is often a demand for extraordinary or impossible results. For example, a demand is often expressed for a form or variety of catgut of which it can be said that a certain size will, when imbedded in the tissues, be absorbed without any extraordinary reaction within a specified time. It is often demanded that a small, weak strand shall be made to withstand the strain of joining a severed muscular tissue until the wound has united sufficiently to no longer need the aid of the suture, and that then the strand of catgut shall disappear. One writer tells of an ideal strand of catgut in an ideal wound which, after serving its purpose of holding the tissues together until firm union has taken place, "is silently and perfectly removed by the activity of the living cells in the patient's body." Another enthusiastically speaks of a suture which at the end of a given time is absorbed and disappears "as does the dew before the rising sun." Demands of this character, however, are not based upon experimental evidence. Positive experimental evidence is very meagre and for the most part unsatisfactory.

In any attempt to explain what happens when a strand of catgut is sewn into living flesh we are beset with difficulties. The work must be done upon animals and not upon man. Observations can be made at intervals only. The naked eye gives little or no indication of the process. Microscopic examinations can only be made after removal of a section of the tissue. It would be impossible to establish any continuous study because the process extends through days, even into weeks of time. No two animals react alike; hence work cannot be exactly duplicated.

The processes are highly complex, involving the whole range of injury—inflammation, wound repair and wound healing.

Taking advantage of the knowledge which has been developed by research in cellular pathology and assuming for the purpose of explanation the correctness of the theories propounded, we offer the following as a plausible insight as to what may happen—when a strand of catgut is imbedded in the flesh tissues.

If a surgically clean knife or needle is passed into the tissue of a living animal (the tissues themselves having also been rendered

aseptic), providing no large vessel be injured, repair will take place rapidly—union by first intention. In such a case the pre-existing cells of the injured tissue do their work with a reaction so slight as to scarcely be observable. Such a sequence of events occurring when the injury to the tissue is of the mildest form, and when the events which follow are normal, is of common occurrence in modern surgery. If, however, an aseptic needle carrying an aseptic thread of silk, linen or like material should be passed into and through the living tissue, and a portion of the thread be allowed to remain imbedded in the tissue, we have introduced a foreign body that must be cared for. It is a very common observation that an aseptic piece of silk or like material becomes encysted without noteworthy reaction and remains indefinitely in this condition, the tissues walling off the foreign body until the injury has been repaired by new cells.

In the case of implanting a cord of catgut into animal tissue, we have introduced new elements. Catgut is an animal substance—collagen (organized gelatin); implanted within the tissue and left to itself, it would decompose and become an irritant. The intention of introducing such a substance by the surgeon is that it shall perform its office as a ligature or suture for a required length of time and then be removed through agencies within the tissues themselves. It is a substance susceptible to disintegration and dissolution—it is an absorbable body—a food substance, and as such is dissolved, digested and assimilated by the cells of the injured body.

We may here observe that in the process of catgut disintegration and absorption there is abundant opportunity for the growth of bacteria should any be present in the tissues, or by accident should the wound become infected from the outside.

The process, however, is not a simple one. In our animal experiments it was found that when strands of plain sterilized catgut were placed in the peritoneal cavity of rabbits or buried in muscular tissue there is at the end of five or six days a beginning of the process of disintegration; the ligature untwists and the interspaces fill up with a cellular infiltrate.

As the process proceeds the edges of the ligatures show evidence of solution, and the cells infiltrate in between the separating strands. These strands gradually dissolve, and in the later stages disappear entirely.

After varying periods (generally fourteen days) there is considerable evidence of the reparative processes which follow; the exterior of the ligature is covered by newly-formed connective tissue, and the connective tisue cells begin to penetrate into the interior of the mass.

After the ligature is dissolved the process appears to run a course parallel with that of ordinary tissue repair, and the whole area occupied by the ligature is finally replaced by newly-formed fibrous tissue.

The disintegration of the ligature itself seems to be brought about by enzymes which are either brought to the place by the blood stream, or, what is more probable, through enzymes generated by the infiltrating cells.

The whole process therefore involves the dissolution and the digestion of the catgut strand and the resorption of the products of such digestion and the building up of new tissue, in short there is involved the whole process of wound repair.

The Integrity of Catgut.

Catgut, especially by reason of its complex nature, is often made the scapegoat for ill surgical results, however the clear, analytical and open mind of the surgeon is always ready to make further deductions when catgut and its use is presented from a standpoint other than that which possibly prompted a somewhat hasty diagnosis resulting from an exasperating situation.

Just so long as catgut is catgut, a product of an animal tissue, it is fair to assume there always will be some grounds for complaints, for notwithstanding the amount of care that has been exercised by the conscientious manufacturer there is embodied the unconscious abuse to which it is so frequently subjected, and an even greater problem presented by the individual equation.

Fortunately, though, complaints in regard to catgut are not as numerous as the complexity of the product would seem to warrant, nevertheless in any attempt to tabulate these according to ratios, troubles concerning tensile strength easily predominate.

An examination of additional strands of catgut, selected from the same batch as those that occasioned the complaint reveals in a vast majority of instances that the material is above the average strength, so that any attempted investigation should be guided by an understanding of the part played, equally from the "catgut's side."

It is easy to unconsciously abuse catgut.

A few sudden jerks by the surgical nurse, ostensibly for the purpose of testing the strand before handing it to the surgeon is equivalent to the method adopted by the grocer in breaking the cord on his parcel—the result is, either the catgut fails completely, or else it is so weakened as to part under slight tension when in use.

Prolonged soaking in aqueous solutions, especially if they be hot or even warm causes a partial gelatinization and a material reduction in tensile strength.

The frequently unavoidable (although sometimes unnecessary), "sawing down" on the knot when the surgeon commences to tie his ligature at a distance from its final resting place, gives rise to some degree of trouble due to the friction caused by the rubbing of the two approximating surfaces, of the free ends of the ligature.

Then again, there exists an unconscious desire to exert extra tension on the second throw of the knot, with the inevitable result that since the first throw cannot be overtied, if it has been properly tied, the extra pressure only serves to cut the strand.

Then, too, if a ligature tube has been badly broken, or the catgut carelessly removed, it is liable to be cut by the broken edges of the glass.

Another complaint that manifests itself is due to the difficulties presented by the stiffness of the strand—a method of softening has already been suggested, but further in this connection it is well to remember that catgut is rendered soft only to the extent of the moisture it is allowed to retain, for this reason many manufacturers produce a nonboilable tube containing a tubing fluid with a moisture content.

Catgut in boilable tubes is invariably stiff.

Catgut in nonboilable tubes is soft and pliable.

In making comparisons for tensile strength the investigator would do well to avoid the marking of a label as an indication of size and instead make a comparison of size for size in accordance with some recognized or standard gauge.

Due to the confinement of a long length of catgut within a comparatively small space, the coiling that is necessary creates bends, or kinks, which are sometimes objectionable—these can be readily eliminated if the surgical nurse will take each end of the strand between the thumb and forefinger of each hand, and subject it to a light even pull.

One of the least registered complaints, yet one that demands the most rigid investigation, arises when the integrity of catgut, from a sterilization standpoint, is questioned.

In an effort to arrive at the cause through a process of elimination, the hospital, or some qualified bacteriologist should be called upon to conduct both aerobic and anaerobic tests while the manufacturers should be made famliar with the fullest data surrounding the cases in which infection occurred—however, aside from this it might be well to acquaint ourselves with a few of the countless little sources of infection that often spell disaster.

The hurried or improper sterilization of the outside of the tube leads to an indirect contamination of the nurse's gloved hands and subsequent handling of the contents results in contaminated catgut.

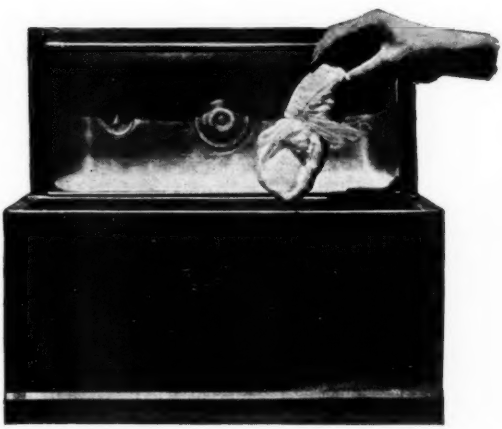
An objectionable method of disinfecting the exterior of ligature tubes. Note that they float and that the upper ends are not immersed.

Then again the strand is occasionally allowed to lie across some unsterile field—even contact with an exposed portion of the skin (which, incidentally, cannot be rendered sterile) may account for trouble—so-called sterile water is not always sterile and sterilizers sometimes need attention while the presence of dust on overhanging fixtures should not be allowed to exist.

Stitch abscesses, minor infections, and even deep infections are at times blamed on catgut, however, while it may be an accessory to the fact, inasmuch as it is a foreign body, it must be remembered there are other contributing causes.

Catgut that is too heavy or not well adapted to the tissues in which it is placed may give rise to catgut indigestion—a suture that is tied too tightly causes necrosis of the surrounding tissue—the tying of too many knots results in an irritation—these create a sequence of inflammation, necrosis and suppuration, while not infrequently a small piece of unabsorbed catgut may be taken from the wound.

Occasionally it is recorded that a strand of catgut absorbed too quickly or failed to last long enough—this condition is therefore largely dependent on the conditions involved, for instance, where a heavily chromicized ligature is indicated neither a plain, nor medium chromicized material will serve the purpose as well, likewise where a medium chromicized strand would be the most adaptable, a more heavily chromicized catgut would be difficult to digest.



An acceptable method of sterilizing the tubes. They are wrapped in gauze, placed in the instrument sterilizer, and boiled.

As to the color of a strand of catgut, it may be here stated that there is a certain amount of variation—this is inherent in the tissue itself, moreover just as there are no two human intestines alike, neither are there two sheep's intestines alike, and when subjected to heat or disinfection each responds differently.

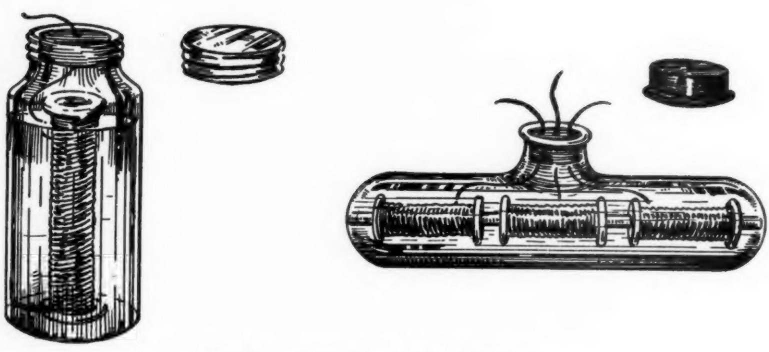
In many instances a change in color is not immediately perceived—exposure to light or long storage may bring about a gradual change, but this darkening is of little moment and should not be made the basis for any complaint.

The Trade in Ligatures and Sutures.

The pharmacist who would make a success of his ligature and suture department must realize that trade in this material is not ordinary merchandising, that he must do something besides deliver a package at a given price. It is one branch of pharmacy where service, backed by technical knowledge, is essential.

If the user is not entirely clear as to the variety of ligature best suited for a particular purpose, the pharmacist must help him make his selection. The maker and dispenser are often blamed for failure when the user is at fault through a wrong selection or error in application. "Let the seller beware" applies with peculiar force to this branch of the trade.

The pharmacist's knowledge must not only apply to prepared ligatures he has in stock, but to other makes on the market, so that if he cannot supply from stock what the surgeon needs, he can intelligently secure it.



Obsolete Forms of Packing Ligatures.

Approved Styles of Packing.

There are two general styles of packing for ligatures—tubes and envelopes. Other styles are simply variations.

Three or four sizes of catgut and silk ligatures are in far greater demand than other sizes. Silkworm gut, kangaroo tendon, silver wire and other forms of ligature material are not in much demand in every-day practice.

Perfection in regard to the methods of packing ligatures and sutures is yet to be attained. Many manufacturers have expressed their own ideas, or have endeavored to follow professional ideals,

with the result that a varied assortment of tubes, bottles, jars, boxes and paper wrappers containing material ready for use have appeared on the market at various times.

Before the advent of the sealed tubes, ligatures were often dispensed in a glass bottle having a cork or rubber stopper, and containing a cylinder around which the ligature was wound. The end of the ligature was passed through the stopper, so that sufficient material for immediate need could be pulled through and cut off, and the balance left intact for future requirement.

Envelope form of packing Ligatures, showing method of removal of strand with sterile forceps.

The tank package was also in favor at one time. It consisted of a glass tube, or tank, containing three glass spools, on each of which was wound a different size ligature material, the ends of which passed up the neck of the tank and through the rubber plug.

Both of these forms of packing lacked a most desirable requisite—the retention of sterility. It was impossible to use antiseptics of sufficient strength to be a potent factor in the attempt to sterilize, and the tanks or bottles containing the preserving fluid could not be heated to a degree sufficient to destroy infecting organisms, especially the more resistant spores.

With this form of packing, even though the ligatures were sterile when originally sent out, their sterilty could not be sustained, as the removal of the cap of the bottle at once exposed the whole top of the container to dust and air contamination.

Ligatures of short lengths, intended primarily for emergency use, and enclosed in triple germ-proof envelopes, have a considerable sale. Their portability—the ease with which they can be transported—finds for them a ready market.

Modern science, through the use of an hermetically sealed glass tube as a container, has evolved a method by which sterility of a suture is maintained until it is required for use. Sterility having been conducted both before and after the sealing of the tube, the tube must be broken before the integrity of its contents can be impaired.

To meet the requirements of various surgical conditions, these tubes are ordinarily prepared in three sizes. Large tubes, holding about ten feet of material, intended for cases in which a large amount of given size is to be used; standard tubes, holding about

Tube Form of Packing Ligatures.

five feet of material, prepared for general operative work; small (or half-meter) tubes, holding only sufficient material to meet an emergency, or where an extra ligature is required to finish an operation.

Special Sutures.

Different types of operations require the use of selective materials. To meet the varying physiological conditions, manufacturers prepare sutures and ligatures for use in special parts. The natural acid secretions and lochial discharges in obstetric cases, for instance, are very destructive to absorbable materials, such as ordinary catgut, and since the immediate repair of any lacerated perineum with an absorbable product is, for obvious reasons, much to be desired, a special obstetric suture, prepared to resist absorption for ten days, was evolved. This is supplied in curved glass tubes, with a large

cutting edge needle attached to the catgut, to facilitate the work in an emergency.

Tubes of obstetrical silk and obstetrical silkworm gut, threaded on full curved needles, are prepared for those surgeons who do not favor the use of catgut for immediate perineal repair.

For convenience in circumcision work, a small-size catgut on a small curved needle, called a circumcision suture, is prepared.

Special sutures are also prepared for use in the cervix, known as cervix sutures; for blood vessel surgery, known as arterial sutures; for suturing the skin, known as skin sutures; for intestinal work, known as gastro-enterostomy sutures. Various types of material with needles attached are commonly called emergency sutures.

A Tube Containing Obstetrical Sutures.

Storage of Ligatures and Sutures.

Sterile suture material, like sterile dressings, should always be stored in a clean, cool and dry place. It is essential that the package be protected from dust accumulations, for wherever dust is present, bacteria is present with it. There is no such thing as dust free from bacteria.

In storing catgut or silk ligatures in envelopes, dampness and moisture must be guarded against. Should moisture be present it may penetrate the paper wrappers and catgut, thereby causing the infection of the contents by organisms through capillary phenomena. This also applies to the storage of surgical dressings.

Handling Ligatures.

The individual tubes or envelopes should always be kept in their containers and never allowed to lie about indiscriminately, either in a drawer or on a tray on a shelf. To store ligatures, or

any sterile articles, in a slovenly and indifferent manner, makes a very bad impression on the surgeon. Being accustomed in his work to carefully observe precautions against all plausible sources of infection, he is bound to notice, and very apt to take strong exception to, any carelessness in storing such material.

When a surgeon sees, on the other hand, that his dealer appreciates the nature of the material, he has greater confidence and respect for that dealer.

One sure way to gain the good will of a surgeon is to convince him that the dealer appreciates some of his numerous difficulties and is trying to help him overcome them.

Commercial Aspects.

Intelligently conducted, the trade in ligatures and sutures will win prestige for any pharmacist. The direct profits may be small in the beginning, but the indirect profits will count on the right side. The pharmacist who masters this branch of his business will acquire a modicum of trade that will give to himself and his store a higher aspect. If the confidence of the profession can be gained in regard to ligatures and sutures, confidence as to everything in the store will be established.

Without attempting to suggest special methods for the advancement of the trade in ligature and suture material, the following are among methods which have been used by pharmacists:

Conferences with friendly surgeons have been sought and secured with a view of gaining an intimate knowledge of the surgeon's views and requirements.

Operations, where ligatures and sutures are applied, have been witnessed in order to gain first-hand knowledge of the subject. The pharmacist always assumes the position of an inquirer, not a critic. Opportunity may arise, however, where he may be able to make a suggestion in a casual, friendly way and score a point.

Pharmacists who are sure of their ground, thoroughly informed on the subject, have been invited to attend meetings of doctors and have explained what they know about the ligature subject. They always refrain from any attempt to dictate or make sales.

Manufacturers' literature is obtained and distributed. Pharmacists realize that it is of little avail, except as a reminder, unless delivered personally, or accompanied with a personal note.

Some pharmacists send out form letters, personally signed.

They have learned that these must be sent with regularity and persistence for best results.

Personal interviews have been found to be the most successful method of developing this business.

Some pharmacists assign one of their clerks to make periodical calls upon all physicians in the vicinity of the store. This method has built up a good trade in physicians' supplies, including ligatures.

Perhaps an occasional sale may be made on price, but real and substantial trade can only be developed through establishing and sustaining the confidence of the physician. It has often required years to gain this confidence, but when it is attained, "it pays."

A CONNECTING TUBE FOR MODIFIED KNORR AND SY FLASKS.

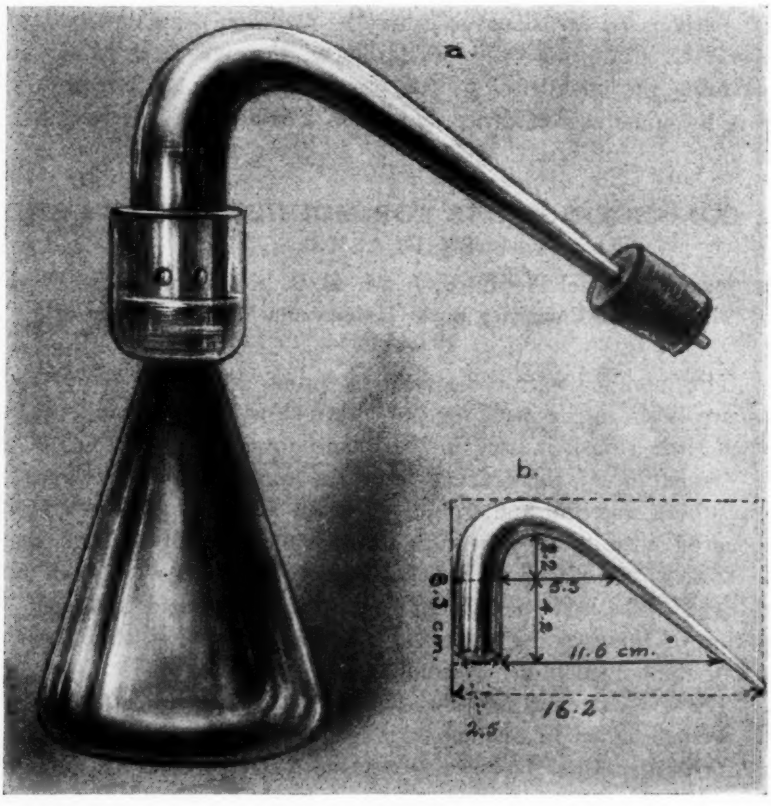
By Joseph Samuel Hepburn, A. M., B. S. in Chem., M. S., Ph. D.
Lecturer on Chemistry in the Hahnemann Medical College of Philadelphia.

The modified extraction flask of either the Knorr or Sy type has two holes in the neck for the return flow of condensed solvent. When such a flask is used in the quantitative determination of fat, the distillation of the solvent after the completion of the extraction is both wasteful and dangerous. The solvent cannot readily be recovered since its vapors escape through the holes in the neck when the flask is connected with a condenser by means of a cork and bent glass tube. If the solvent be inflammable, there is danger of ignition of the escaping vapor. If the vapor be toxic, the evaporation of the solvent must be conducted in a hood.

The glass connecting tube, which is shown in the illustrations, has been designed to overcome these difficulties. The upright arm has such an internal diameter as permits it to fit loosely between the neck of the flask and the outer collar. The joint is sealed by means of mercury just as in the extraction apparatus. The inclined arm is drawn to a small diameter at its lower end so that it may readily be inserted into a bored cork and thus be connected with a water-jacketed condenser and a receiver. The flask rests on a water bath which is heated by either a gas flame or, preferably, an electric stove. In this manner, the solvent may be recovered completely, and danger of ignition of its vapor or diffusion of the latter into the atmosphere is reduced to a minimum. The connecting tubes

used in this laboratory have an internal diameter of 2.5 centimeters at the bottom of the upright arm and of 0.4 centimeter at the bottom of the inclined arm.

The author is deeply indebted to Mr. Erwin E. Faber, who has drawn the illustrations from the apparatus. Figure b is a line drawing of the connecting tube. Figure d depicts the tube resting in



Connecting Tube.

the mercury seal of a modified Sy flask and provided with a cork for insertion into the condenser. These tubes have been used in this laboratory with satisfactory results for over a year. While others may possibly have used this device, the author is unaware of any mention of it in the literature, and has been unable to find such a device on the market.

Constantine Hering Research Laboratory,
The Hahnemann Medical College of Philadelphia.

THE HANDWRITING ON THE WALL.*

By John Uri Lloyd.

The subject of my address is, I believe, of importance. We of the present are interested. Those who are to follow, members of the profession, must be more interested. To me the handwriting is distinct and the letters are plain. There is no longer a doubt regarding their character, and I think that most persons will agree with the spirit of my paper even if differing on certain features of it. It matters not whether the handwriting is as we wish it, or is in substance as we would prefer it. There it stands and stares at us.

Before proceeding, I would call to your attention that my own pharmacy is the result of empiricism, and that when I refer to empiricists in pharmacy, I include myself and others who have stumbled into the profession by irregular labors and interrupted, unsystematic, laborious study. I will not here attempt to argue the final possible result of such labor, but simply state that we have had to do a large amount of work that under proper guidance is, perhaps, unnecessary.

In this regard most of us stand together. We are, as a rule, pharmacists with high opinions of olden time and former methods. We commenced our labors as apprentices or errand boys; we struggled at first with window washing, mortar and graduate cleaning, and perhaps scrubbing the floor. Then we were permitted to learn the weights and measures, to occasionally triturate a mixture in a mortar, to replace bottles after our employer had used them in compounding a prescription, and afterward to even *bring* him shelf bottles to obtain his medicines from, as we watched him fill a prescription. Thus we passed gradually to the weighing of these substances under the eye of our preceptor, the folding and dividing of powders, the measuring of liquids after our employer was sure we could read that particular prescription, and so on to filling prescriptions; few of us had the advantages of a college of pharmacy education. Am I not right? Have we not severally felt the pride of being left alone for the first time in the store? To me it seems that the proudest day of my life was that on which my employer,

*Address made before the Ohio State Pharmaceutical Association, at Akron, June 9, 1887.

bless him, still one of the worthy members of this society, gave me the charge of his store while he left for an entire afternoon.

This is the way we learned the business and in my opinion it is yet the only way to learn a certain part of it. However, those of us who thus reached a creditable position in our profession are confronted with the fact, for fact it is, that the past is not the present. Once we made our own pills, plasters, tinctures, syrups; there were but few fluid extracts and no elixirs. Elegant pharmacy was unknown. Now the plaster iron is nearly as great a curiosity as a hand spinning wheel or the old tin lantern. We purchase our pills ready made and in bottles; our fluid extracts are supplied to many of us without more trouble than the extracting of a cork; tinctures and syrups are more or less obsolete, being replaced by pharmaceuticals that are, perhaps, not made by pharmacists. Are these not facts? Do I overestimate when I say that twenty years only have thus altered our business and our business methods? We have striven to repel the invasion. We have resented each innovation. We have attempted to devise methods whereby pharmacists could continue in the beaten path, but I am now of the opinion we have been combating the inevitable. Do we lament this change? It matters not if we do. Shall we sour upon the world and make it unpleasant to others because of changes that happen in a world where all is change? What benefit follows? The tide is moving into new channels; we must either move with it or drown.

A fish will drown if the current is swift and the fish is forced to stand still and face it. Growling will not help us. Whether we like the weather or not, we must meet it and unless we do meet the changes in methods we will suffer. Have we not examples of honorable and persistent men holding on to olden times, and do we not in every old city note the result? We may crawl into an old-style store; we may keep a jar of snakes and lizards in our front window; we may thrust at each physician that pharmacy is degenerating, and we may growl at the condition of affairs as compared with the olden time. Our former patrons will one by one move away. The aged physician will die. The modern physician will propose to administer what he pleases as he pleases; the modern patron will insist upon getting medicines where there are sunlight and pleasant words; where stationery, perfumery and cigars are sold, if you please, and even candy. Thus we will become a relic of a former period, and our families will suffer, perhaps, because we refuse to

learn that the world will not move backward in the path our preceptor trod. These lessons are everyday ones and painful, too. Struggle as we may, such facts are incontrovertible. Finally we will become sour and crabbed, and either snarl at a few who care nothing for us, and irritate by smiling at us, or will give up the business in disgust. Then our lizards and musty herbs, our snakes and old-style ointment jars will be carried to the dump, and a man of the present (perhaps not a pharmacist, but employing one) will paint the store and modernize the fixtures—will invite the sunlight and the people. A new business will then appear and patrons will occasionally smile as they speak of the peculiar old pharmacist who refused to move on, whom the ladies shunned, the children shuddered at, the men passed by, and physicians detested.

Doubtless the majority of us will modernize ourselves under the pressure of circumstances, and accept the good, old Baptist doctrine of "what is to be will be," and move on with the throng, but I suspect that each locality will have its relic. To me there is something touching in this isolated, quaint and persistent man, who refuses to read the handwriting, covers his face at the present, turns his back to the future, and lives in the past. I view him as a man of opinions and a man of courage, a man who dares to do what he believes to be right, and perhaps suffers to maintain the standing of his profession as he views the matter, and uphold the name pharmacist, where there are, as he believes, so few pharmacists. Do not doubt his honesty. Do not doubt his motives. He is very sincere, and if you will become acquainted with him you will find that from his store of knowledge there is much to learn that you can not get elsewhere, and you will find him far from being cross and petulant, as the world believes him to be. Perhaps he is not even sad, for he may carry in mind the prosperous pharmacy days of former years, and review them with pleasure. He may not be companionless; more than one aged friend will be found to spend hours in his dingy shop, and together they enjoy themselves with few interruptions. In his family he will be found undoubtedly loved, perhaps deemed peculiar, but nothing more, and it may be that you will find that his shop is his recreation, and that he enjoys the apparent misery of his den. You may find that it would be fatal to disturb him. Perhaps some persons may think I have pictured an ideal figure, but others will refer to some friend who may be faithfully portrayed. Not one city, but all that are of any age,

have these connecting links between the past and the future. Not one such man exists alone, there are many.

We look at this picture of the old, old times and forget ourselves. We think that we learned the modern part of the profession of pharmacy, and forget that history repeats itself and that the hand is still writing as in the past; that the years fly swiftly. We think that only the old-style pharmacist can be obsolete, and at the same time we unconsciously growl at the innovations of the young generation. We oppose the new fangled notions, and we may combat the new ideas of pharmaceutical education, and compare them with the day we were apprentices. Some of us may oppose college learning and complain because pharmaceutical journals thrive and multiply, referring to the time in our younger days when one journal, issued once in two months, was sufficient for the country, and but two colleges of pharmacy struggled for existence. We may even sneer at the terms Ph. D and Ph. G., and begin to travel in the old, old path that leads to grumbling at everything modern, and eventually to an isolation where we will serve the coming generation as a zoological specimen, perhaps doing good in an educational manner, as exhibiting the difference between the pharmacist of the past and the present.

I would not have anyone think that this is written as a trivial matter. It is not. I am not disposed to make light of such facts, and in my description I have endeavored to confine myself to what I view as facts. I would not thrust a pin into myself as I do when I think of the progress (?) in directions that rubs against the grain, because it is painful to the flesh. It is necessary though, I think that we should look at ourselves occasionally, and I ask if we are not traveling the beaten road. Do we not criticise the present methods of filling our stores with sugar-coated pills, with gelatin-coated pills and capsules? Do we not often oppose the ready-made plaster, and lament the days so recently passed away, when pharmacists were pharmacists? And do we not sometimes attempt to devise methods whereby the hands of time may be turned backward and the old styles detained? Do we not think of the time when a few officinal syrups and tinctures, with our staple chemicals and crude roots, barks and herbs, supplied us material with which to fill all prescriptions? Do we not sometimes in a period of vexation sneer and snarl over these (to us, useless) so-called elixirs of the present, and do we not get out of patience when physicians pre-

scribe a preparation made by some particular person, not in our opinion a pharmacist, to the neglect of our own preparation, that in our opinion is better?

Have not some of us tried to check the wheels of progress (in our opinion so-called progress), and have we not occasionally limped to our dens with a crushed toe while the wheels rolled on? Is it not true that many of us have fruitlessly opposed these innovations as they have swept over the country, and that we have viewed with detestation—perhaps still do—the great factories where men who perhaps, never have pretended to be pharmacists, make medicaments and then under our very protests force us to use them? Have we not sometimes become irritated at a gentlemanly solicitor whose every attempt to dispose of his wares demonstrated the fact that he was not in the least acquainted with the first principles of their production or properties, and yet whose unpleasant duty it was to travel over the country to encourage us to use them instead of our own?** Have we not more than once rebelled, and is it not usually to no purpose? I am speaking now to a body of pharmacists who, as a rule, must perceive that these are facts. We stand together, and I, for one, realize that slowly but surely we will become antiquated if we refuse to move onward, and that we must struggle to prevent ourselves from becoming covered with incrustations and to avoid fossilization.

We must take the pharmaceutical journals—not one but several. We must read and study them; and there is something to be learned in the advertising columns as well as in the body of the journals. We must study indications, and take advantage of each twist of the weather vane.

The majority of us will be able to pass on with credit. We must do so if we keep in the path, but it will require an effort, while doubtless here and there an obstinate man will step aside and cling tenaciously to the olden time, and serve the coming generation with an example of a pharmacist of other days. We must accept that our pills, ointments, plasters, chemicals, flavors, perhaps even some emulsions, syrups and tinctures, will be made for us by men

**More than once I have shown a solicitor the error of his belief, or have endeavored to interest him to his advantage. Sometimes these interested gentlemen have gone with me to my laboratory, and have been thankful for the attention. Traveling agents, as a rule, are gentlemen. They learn and teach and help to move the world of commerce and of ideas. In turn I am often instructed by them.

we call artisans. We must become artisans if we compete, and we must, perhaps, adopt their methods or perish as progressive pharmacists.

Our future field as pharmacists seems to be in mixing and supplying such substances as we can carry to advantage in our stores, unless the science broadens, or we step aside into specialty-making; and to oppose these innovations seems to be to slap at the hand of destiny that is writing on the wall, so that he who runs may read. To many these changes in our profession are unconscious and uncared for, but to others they are painful, very.

I am led to these remarks by the seemingly universal feeling among old pharmacists that the profession is becoming demoralized. The change has not been abrupt. It is gradual, but as we make comparisons between intervals of time it appears to have been by jerks. In my opinion, we must be prepared to meet as great a revolution—advancement or retrogression, as you view it—in the near future as in the past. I can see that we shall continue to suffer, and those who rebel will do so at the expense of aching hearts. That our profession is not in a condition to rest on its oars is evidenced by the attention which physicians give to new ideas and remedies; by the facility with which the grocery or dry goods men adapt themselves to the absorption of sections of pharmacy, or so-called pharmacy (which lives, nevertheless); by the obsolete remedies of the past and those of the present which are nearly stagnant on our shelves; by the synthetical chemicals (patented, if you please), that are displacing nature's products, and that take from us a demand for old-fashioned pharmaceutical manipulation. These and other causes lead us to believe that unless we move quickly we will fall behind, and that instead of kicking against the pricks, it behooves us to be graceful and accept that the hand of destiny is writing.

Finally, I will add that those who oppose this continual change are, as a rule, in my experience, the best pharmacists, educated, thinking men, who have a foundation for their arguments, whom all should honor, and in no wise should their earnestness be questioned. Often—usually—these men begin the study with superior education, and maintain their position to the end, and are aware of their advantages. I venture to say that in nearly every instance it will be found that these tenacious men are well informed, and that it is not because of ignorance or indolence that they refuse to grace-

fully accept present methods, but because of honor to themselves and respect for their profession.

Some live in constant hope that the pendulum will swing back again, but I will confess that it seems to me the past will not return in this generation. The methods and means by which medicines are made, sold, prescribed, advertised and dispensed, appear to me to pass, each year, further from the accepted legitimate pharmacy of other days, and with irresistible motion.

ABSTRACTED AND REPRINTED ARTICLES

THE PANCREAS GLAND.*[1]

The Research and Applied Chemistry of Its Digestive Enzymes and Its Internal Secretion Principle.

By Benjamin T. Fairchild.

The applied chemistry of the pancreas internal secretion is at this time a subject of special interest to those engaged in the production of medicinal preparations, particularly of the animal gland and endocrine organs; for the one-time hypothetical internal secretion principle has become, in the form of a hormone extract free from the digestive enzymes, a recognized therapeutic agent as an antidiabetic remedy.

Reagents for Hormone Extraction.

It is, of course, well known that the fundamental reagent of the hormone extraction is alcohol. Alcohol has, in a peculiar degree, these desirable properties—it is a precipitant of the enzymes, a precipitant of the coagulable proteins with which enzymes are associated (and thus both may be thrown down), and also for the extraction of certain associated nitrogenous substances not primarily coagulable; and, finally, it is a means of obtaining the sepa-

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[1] Presented before the Division of Chemistry of Medicinal Products at the 65th Meeting of the American Chemical Society, New Haven, Conn., April 2 to 7, 1923.

ration and precipitation of the more isolated principle (hormone) in a form in which it may be readily taken up, in a menstruum suitable for injection or for other purpose.

It is the pancreas gland proteolytic enzyme, its behavior *in vitro* with the other constituents of the gland and with alcohol, which is the chief concern here, particularly the production of the pancreas hormone principle.

The very first steps in the discovery of the existence of the enzymes, their separation, and, so far as attainable, their isolation from the gland, were made by the use of alcohol. And here one immediately must recall Kuehne's well-known studies of trypsin. Kuehne and his associates are credited with the discovery of this proteolytic enzyme, and to them we owe the name. His process for the preparation of trypsin, in brief, amounts to the precipitation of infusions of the gland by alcohol in excess, taking up in aqueous solution the alcohol precipitate which contains the trypsin and the protein to which Kuehne gave the name "leukoid." Then follow the successive acidification and alkalinization for the separation of these associated substances, and repeated precipitations and further purifications by dialysis and precipitation by alcohol; the whole series of processes being repeated several times if necessary.

In this connection we find experiments, particularly of Kuehne and Chittenden, directed toward determining the nature of the protein substances associated with trypsin in this form, and in which acids and alkalies were employed for the successful separation. One who has occasion to observe the behavior of alcohol with organic extracts, pancreatic peptones, autolyzed extracts of the glands, will have become familiar with this fraction or residue of nitrogen substances, not directly coagulable, which are now recognized to be largely peptone, polypeptides, and amino acids.

The use and action of enzyme and protein precipitants—ammonium sulfate, phosphotungstic acid, etc.—are also now familiar. The influence of acid upon the pancreas proteolytic enzyme, both its activating and its destructive action (according to the percentage used), is well known.

Since these early days the behavior of alcohol with enzymes and proteins has, of course, become well known, and alcohol is commonly utilized for these preparations in applied chemistry. Starling used alcohol in his final preparations of his original first-discovered hormone, secretin, from the duodenal mucosa. Alcohol was also em-

ployed by Takamine in his process for the isolation of the adrenal hormone. Undoubtedly, all this work with alcohol must have influenced the methods of its use, not only in the discovery, but in the practical separation of vitamins.

The use of acid is also well known in methods of precipitation of various substances, its influence upon the behavior of the proteins, the precipitates; also in the processes of extraction of the hormones and vitamins, its activating influence upon the latent principles—for example, by Pawlow and his colleagues for the activation of the duodenal mucosa internal secretion, and by Starling in obtaining this principle, his duodenal hormone.

Analogies between the vitamins of food and of the gland and the hormones are naturally suggested to those interested in this subject and undoubtedly must often have been a subject for consideration. They are of particular interest in this connection because of the presence of vitamins in the glands, notably in the pancreas, and in the methods employed—for example, by Eddy-Roper in the acid-alcohol extraction of the pancreas gland vitamins. Here it might be suggested that such preparations of the pancreas demonstrably containing the hormone may also contain the vitamin; also as to whether the more drastic methods for the separation of the vitamins may not, at the same time, destroy the hormone of the pancreas. However, the procedure in all this is on definitely related lines, fundamentally the employment of alcohol and acid.

Preparation of Entire Pancreas Gland Products Containing Active Enzymes.

It was natural that the enzymes of the pancreas should have first received attention as demonstrable substances of its external, obvious digestive secretion. The writer's early work was directed toward the preparation of entire pancreas gland products which should contain the proteolytic and other enzymes in their most active form, yet with other constituents of the entire gland substance with which the enzymes are normally associated. It seemed that these preparations might be indicated, and be of service, in the treatment of certain forms of diabetes and glycosuria, as well as obviously of value in cases of disturbance of digestion and metabolism clearly associated with deficiency of pancreas digestive enzymes.

As the perception of the existence and importance of the internal secretion grew the writer came to advocate more massive doses

and at frequent intervals, this with the thought of more adequately supplementing a secretion which is continuously poured out and which must at any time contain but a minute quantity of the active hormone principle. It was also evident that an extract containing at least four different enzymes and associated substances must contain but a small and probably inadequate quantity of the internal principle. The entire enzymic gland extract might also present some defects for the treatment of diabetes mellitus in consequence of a possible deterioration of the hormone under the influence of the proteolytic enzyme in the course of the preparation of the extract.

Experiments With "Internal Secretion" Extract.

Later, in the consideration of the classic experiments of the gland extirpation and implantation, the writer was led to prepare and to offer "internal secretion" (hypodermic) extract from the entire pancreas gland, demonstrably free from the digestive enzymes and designed to contain the active principle of the internal secretion, a hormone extract of the pancreas.

In this procedure there seemed to be the one logical means of the solution of the clinical problem clearly suggested in these experiments in animal diabetes—either to realize its possibilities, or to establish the impossibilities, of clinical application, for the results of the implantation of even a small portion of the extirpated gland seemed to show that the structure conveying the active principles must be throughout the substance of the gland. The conditions were such as to exclude any possible participation of the enzymes in the physiological effects observed, so far as metabolism of the carbohydrates was concerned; the enzymes of the transplanted gland became simply so much negligible inert substance, and, indeed, probably in a state not only inactive, but inactivable. The antitryptic role of the blood (a defensive factor) raised by trypsin itself when introduced into the blood may also be recalled here.

The injection of an entire pancreas gland extract (of the normal animal) prepared by methods which would exclude the enzymes would clarify all the problems and definitely answer the crux of the clinical problem involved.

The experiments in animal diabetes, the injection of pancreas extracts of the gland of the depancreatized animal, however confirmatory of the hypothesis of the internal secretion, could only the more inevitably suggest this clinical expedient—the injection of

hormone extracts of the entire normal gland of the normal animals upon the diabetic man, the injection free from enzymes immediately excluding any possible role of the enzymes. This exclusion of the enzymes to be readily accomplished by alcohol precipitation, and such use of alcohol (in connection with the first step in the treatment of the fresh gland) as to keep the proteolytic enzyme in abeyance, prevent its action upon any associated substances of the gland. It was indeed quite unnecessary to undertake any procedure for the destruction of the enzyme, for this involved the possible destruction, or at least weakening, of the hormone.

The author's years of experience in the use of alcohol in the preparation of the enzymes of the pancreas gland had involved a study of all the conditions under which alcohol might best be utilized to hold the enzymes in abeyance, its influence as a destructive agent, as a precipitant, and its action upon the albuminous and complex proteins of the fresh gland and infusions of the gland. All this clearly indicated that (in connection with the whole status of the subject) in alcohol was a means of obtaining a solution suitable for injection, which should, presumably, contain the active hormone principle, demonstrably free from digestive enzymes and coagulable, precipitable substances.

Whatever view might be entertained as to the therapeutic possibilities of such a hormone extract in diabetes, there existed no risk, no serious obstacle to such use by injection as might determine its antidiabetic properties. For it happened also that the writer's attention was early engaged in the preparation of pancreas gland extracts designed for hypodermic use, this having been a subject of inquiry in connection with certain diseases of metabolism. He prepared such extracts designed to contain enzymes with the soluble constituents of the gland; also an extract designed to contain the soluble gland constituents with amylopsin, and to a large degree separated from the proteolytic enzymes. He prepared pancreas gland injections of definite trypsin potency, and these were originally prepared so as to present the trypsin as extracted directly from the gland, with the associated soluble cell constituents free from amylopsin and lipase. Later with the desire of greatly increasing the tryptic potency, the injections were prepared directly from the most potent isolated trypsin attainable. These trypsin and amylopsin injections were originally prepared for Dr. John Beard, of the University of Edinburgh.

Some of these, the enzymic, preparations not being suitable for sterilization by heat, an attempt was made to ascertain whether by the most rigid methods of preparation and then the Berkefeld filtration, it might be possible to obtain a preparation so sterile as to be fit for injection—an attempt which was successful.

In view of the thought which then existed as to the dangerous action of the various complex proteins by injection, and the sometimes assumed essential toxicity of an enzyme itself, experiments were made in the injection of these various protein and enzyme-containing substances (extracts, solutions) upon animals. These experiments showed that all these injections produced generally favorable results rather than otherwise—in quantities far beyond clinical usage.

In the clinical use of all these injections there were observations and comment as to the generally beneficial effects, the generally increased well-being of the patient; and the belief was expressed that local bad results, of rare occurrence, were not to be attributed to any direct influence of any constituents of the gland injection; rise in temperature, etc., were naturally to be guarded against. On the score of protein or derivatives thereof as contained in the injections, there appeared, therefore, no serious objections to the clinical experimental use as proposed, with due precaution.

At the outset sterilization by heat was sometimes used in making the preparations designed to be enzyme-free; but soon alcohol came to be relied upon, for reasons already made evident, and thus the possible hazard of destruction of the hormone was avoided.

At that time the writer was not aware of the long previous use of a direct pancreas extract by hypodermic injection, without bad local results, by Dr. S. Solis-Cohen and his colleague, Dr. Knipe, of Philadelphia. This extract was aseptically prepared with no thought of excluding the enzymes. Under the circumstances, it is interesting to quote from a paper on this subject as long ago as November, 1893:[2]

> "No bad local effect, such as digestion of the tissues or abscess, as I at first feared might be the case, was produced in a preliminary trial upon animals and upon himself, kindly made by our former resident physician, Dr. J. C. Knipe; and none resulted in our patient. The thirst diminished; and as less water was ingested less was excreted; but we observed no constant or decided effect upon the quantity of sugar excreted."

[2] Solis-Cohen, "The Therapeutic Properties of Animal Extracts."

Incidentally, Dr. Solis-Cohen pointed out that, aside from their nutritive properties, preparations of animal organs and tissues may have two different kinds of action in the human body: (1) "when they replace some normal secretion deficient in the patient," and (2) "when they act as any other drug, modifying function and tissue without relation to the nature or physiological purpose of the tissue from which they have been derived."

As early as 1903-1904 the writer prepared internal secretion preparations of the pancreas by means of acid and alcohol extraction, the final solution of the hormone substance sterilized by the Berkefeld and put up in ampules; also for oral administration. In 1906 the first statement concerning this preparation of the pancreas gland designed for hypodermic use was published:

> "Internal secretion (hypodermic). A sterile pancreas solution containing the soluble constituents of the fresh gland free from enzymes, in sealed glass tubes for hypodermic use."

The first physician of whom the writer has record as suggesting the clinical use of a pancreas gland extract free from enzymes was Dr. W. M. Crofton, then Lecturer in Special Pathology, University College, Dublin.

In a report[3] of the successful treatment of a severe case of glycosuria (diabetes) with the whole pancreas gland extract holadin, Dr. Crofton states his "conclusions on physiological, pathological and clinical grounds and the hypothesis which led him to propose for clinical use in diabetes an extract of the pancreas from which the external secretions, trypsin, amylopsin and lipase were removed." He also gives the history of a case in which he employed this new "internal secretion," and describes the results, both by mouth and injection:[4]

> "The increase of strength under the use of the whole extract (Holadin) was very marked and the increase when this was changed to the internal secretion was quite as noticeable."

This "internal secretion" was freely placed at disposal and the reports were of such an encouraging tenor that it was made available under a title which would indicate its hormone nature—"hormonadin."

[3] *Lancet, 176,* 607 (1909).

[4] "A New Pancreatic Extract in the Treatment of Diabetes," *Dublin J. Med. Sci.,* May, 1910.

Dr. Crofton says of hormonadin: [5] "I think all my patients have been benefited by it and I did not restrict their diet." He personally advised the writer of his experience and his belief that the internal secretion (hormonadin) definitely controlled the sugar, increased the tolerance for carbohydrate, and was generally beneficial, but that the results were transitory, which would seem to indicate that the patient might have to take hormonadin for the rest of his life; and he expressed the hope that this extract might be made as cheaply as possible.

Some years later, Dr. Solis-Cohen, who had long been interested in the subject, personally wrote in almost precisely the same terms concerning his experience with hormonadin injection, and particularly commented on its transitory effects, which indicated the necessity of its continued use, although he considered this a great desideratum, especially in view of the increased tolerance for carbohydrate. He used it hypodermically and by the mouth.

Quite recently, in a discussion of the effects produced by the pancreas extract, insulin, at a meeting of the Association of American Physicians on May 3, 1922,[6] Dr. Solis-Cohen mentioned his experience, with his colleagues, on the oral and hypodermic use of a hormone pancreas extract (alluding to hormonadin) and with such a degree of favorable results, by no means in all cases, as to encourage continued use.

Inasmuch as the pancreas hormone preparation was submitted both for oral administration and injection, it should be said that it has not so far proved possible by ingestion by the mouth to obtain demonstrable effective reduction and control of blood sugar in experimental or in clinical diabetes, so that at present reliance must be upon the injection—this despite some results of experiments, and the hope which was entertained and anticipations which might be formed in consequence of experience in the use of the thyroid. The hormone of the pancreas extract is rendered inert *in vitro* by pepsin and by trypsin. Nevertheless, the writer feels that the last word concerning the oral administration has not been said. There has been a rather extensive use, by the mouth, in the treatment of glycosuria going on for several years and in the hands of a few physicians only, and of one physician continuously for the past few

[5] "Pancreatic Tissue, Metabolism and Diabetes," *The Prescriber* (*Edinburgh*), April, 1913.

[6] *Trans. Assoc. Am. Phys.*, *37*, 345 (1922).

years, the results of which are impressive and would seem to require and justify further clinical study from the vantage point of our present knowledge.

With the progress and practice in the differentiation of various types of diabetes—this in consequence, indeed, of the research, laboratory and clinical, brought about by the study of the hormone extract—there will undoubtedly be a thorough trying out in all types of diabetes of all possible definite potent pancreas gland extracts.

The very limited clinical use of this hormone injection is to be noted; indeed, it is significant that during these years practically no inquiry or general interest had been elicited.

In 1910 hormonadin was simply placed upon the list of pancreas gland preparations and definitely described:

> "An extract of the pancreas cells containing all the soluble chemical and noncoagulable principles of the pancreas, free from trypsin, amylopsin, and lipase. Hormonadin is therefore an extract designed to contain the principles of the internal secretion of the fresh pancreas gland in a purified sterile solution. This special preparation has been for a considerable time supplied for clinical investigation for the purpose of exhibiting the peculiar principles of the pancreas cells believed to be essentially concerned in metabolism. It is offered simply with a view to forwarding this subject which is in a purely experimental stage. This in ampules for hypodermic injection; and for oral administration."

This publication (submitting hormonadin for purely experimental clinical use) was continued until 1921, when it was withdrawn with the intention of including it in some future separate description of pancreas gland therapeutic preparations, in order to include a new preparation of the pancreas gland.

That interest in the subject of the pancreas gland in its relation to diabetes which led to the preparation of the hormone extract had also drawn the writer's attention to the studies of the glycolytic action of pancreas juice and extracts upon sugar in the presence of fresh blood. For about six years he has had this subject under research and experiment.

The difficulties which have been presented in the laboratory for the actual proof of the existence of this principle, its assay, and the controversy on this subject, are well known; but it is now quite certain that a principle (in an extract of the pancreas) has been obtained, which exerts glycolytic action upon sugar when this is added to fresh blood *in vitro,* and in which participation of any bacterial

action or attribution of this behavior to other chemical reaction is excluded. The glycolytic principle as contained in this pancreas extract is resistant to the action of the pancreas proteolytic enzyme *in vitro*. It is resistant to the gastric proteolytic enzyme, as shown by submitting this glycolytic extract to contact with artificial gastric juice—pepsin, 0.3 per cent. hydrochloric acid—*in vitro* at 37° C. It has no direct action upon sugar *in vitro*. As contained in this pancreas extract, in aqueous media, it is killed by boiling.

This glycolytic pancreas extract corresponds in these respects, in the behavior of its glycolytic principle, with that observed by Clark of his pancreas perfusate.[7]

In vitro the writer found his hormone extract of the pancreas practically free from this glycolytic property, and now this is confirmed of the most potent hormone injections. The ordinary official pancreatins are for the greater part negative as to glycolytic action.

This principle is found in a rather richer degree in the tail portion of the pancreas gland and this particular portion for the glycolytic product is preferably employed. Clark, from his experiments with "pancreatic perfusates" in "heart and pancreas and sugar metabolism," is led to express the conclusions "that the pancreatic factor concerned in the glycolytic action observed possesses some of the characteristics of an enzyme; has more of the characteristics of an enzyme than of a stable internal secretion like that of the adrenal glands." The function of this principle, its actual relation to the antidiabetic mechanism, so far presents an unsolved problem.

This product has been under experimental clinical use, and with results which indicate that it is of therapeutic value, but the further mention of which would be aside from the scope of this paper.

Becoming interested in the peristaltic hormone, the writer's attention was directed toward a patent by Zuelzer for the preparation of this hormone, and he was surprised to read that Zuelzer had obtained also a patent for the preparation of the "pancreas hormone"; therein he states:

> "This pancreas ferment, rather hormone, was discovered as the agent for normal glycolysis, and the production of such ferment is described in my application for patent, serial number 431,226, filed May 6, 1908."

He found that the specification as described in Zuelzer's application, May 6, 1908, patented August 6, 1912, covered this inven-

[7] *J. Exp. Med., 24,* 621 (1916).

tion—"A non-poisonous preparation, a pancreas preparation, suitable for the treatment of natural diabetes," in which alcohol was employed for the killing and removal of the enzymes trypsin, steapsin, and diastase, and the precipitation of albuminous substances, "the final preparation being free from ferments and in its best form gives none of the known protein reactions."

This Zuelzer preparation was also standardized by the action of a definite quantity of his final product by hypodermic injection against induced adrenalin diabetes.

The prior preparation and publication of the writer,[8] as has been herein described, renders this antidiabetic pancreas product and process without restriction for general availability. Broadly, Zuelzer's patent for an enzyme-free antidiabetic preparation had already been anticipated; likewise the employment of alcohol as the fundamental principle for the removal of the enzymes and for the purification from albuminous substances.

Indeed, the idea that the digestive enzymes might be unfavorable (destructive) to the hormones *in vitro* must often have suggested itself, and appears in the literature of the subject. Cohnheim, for example, referred to it, and Zuelzer employed alcohol for the exclusion of the enzymes in his animal diabetic experiments, and made this a fundamental factor in his patent specification. On this subject Clark remarks:

> "The obvious objection can be raised to all such experiments that in grinding the pancreas its powerful proteolytic enzymes might readily inactivate a more delicate product of internal secretion."

Scott[9] employed injections in the preparation of which the external enzyme was "first inactivated by a high percentage of alcohol" and later "killed by high percentage alcohol"—contact long continued with heat. Crofton's suggestion has already been mentioned.

The experiments of von Mering and Minkowski, so frequently repeated and finally with complete confirmation of the original experiments, evoked experiments in which intravenous and subcutaneous injections upon depancreatized dogs were substituted for the original procedure, a physiological research primarily directed with

[8] "Pancreas Internal Secretion," 1906.

[9] *Am. J. Physiol., 26,* 306 (1912).

the purpose thoroughly to scrutinize or establish the internal secretion hypothesis.

The literature of this subject shows the history of years of work on the part of many individuals and, in some instances, of experiments continuously carried out during several years.

The clinical purport of these experiments, which, if successful, should point the way to clinical expedients, was also discussed. Kleiner's studies and investigations [10] are especially interesting and pertinent in this connection:

> "It is evident that the demonstration of a beneficial effect of a pancreas preparation, when administered parenterally to a diabetic animal, would be of importance, both theoretically and practically. Theoretically it would support the internal secretion hypothesis of the origin of diabetes. Practically it would suggest a possible therapeutic application."

His paper embraces an important valuable review and critique of the earlier work and a discussion of the subject. "In view of the unknown nature of this internal secretion principle, he employed "direct aqueous infusions of the fresh pancreas." In some cases the "pancreas emulsions injected resulted in changing a pronounced hyperglycemia to a normal blood sugar." This, as well as the previous work of this author, was in the main successful, and "regarded as further evidence of the internal secretion theory of experimental diabetes." Referring to unsuccessful attempts at pancreas therapy, he states that "the methods heretofore used have not resembled the one used in our experiments." He questioned whether filtered extracts would be effective, and "particularly whether an emulsion of the pancreas of another species would have this effect when injected into a diabetic dog." (It is of interest here to note that this had already been done, and this question answered, by Zuelzer.)

A careful study of the whole subject will reveal that these many experiments, to a remarkably uniform degree, go to confirm this hypothesis of the regulation and control of the metabolism of the carbohydrate. The temporary nature of the reduction of the blood sugar was uniformly reported.

These pancreas solutions for injections were made in a variety of ways—acid, alkaline, neutral, some directly from the tissue juice, some alcoholic extracts. In no instance was there a net result

[10] *J. Biol. Chem.*, *40*, 153 (1919).

which led to a conclusion contrary to the internal secretion hypothesis. That discrepant and varying results, or accompanied by untoward manifestations, might be accounted for by the nature of the injections employed, the method of their preparation—for example, use of unfiltered extract—was frequently suggested and discussed.

Strong alcohol and heat are distinctly injurious to the hormone, and this is particularly true in the presence of acid, as used in some of Scott's experiments. A direct aqueous tissue juice of the pancreas, or infusion of the gland, slightly acid, or feebly alkaline, may contain an enzyme in an active form, or in a latent state which will become active upon standing, and therefore an injection originally active may prove to be weaker or perhaps inert in subsequent experiments, after exposure at ordinary room temperature by contact with the proteolytic enzyme.

The enzyme as a constituent of the injection is simply so much protein without interference with the hormone action other than as one of the (complex) proteins of the injection. There was no evidence adduced, no reason found, to attribute toxic properties to the hormone principle itself.

With the immense study of the physiological chemistry of the pancreas, the conception of the dual nature of the gland mechanism, the peculiar structure of the pancreas gland substance to which Langerhans attributed the property of the internal secretion, "the gland within the gland," became an accepted hypothesis.

In 1898, in "The Textbook of Physiology," edited by E. S. Schafer, occurs this statement:

> "This clearly shows that the diabetes which results from pancreas extirpation is exclusively the result of something belonging to the gland which acts independently of its function with digestion."

As early as 1893 Gamgee, in his "Physiological Chemistry of the Animal Body," states:

> "In addition to this whole obvious function, the pancreas plays a remarkable and as yet incompletely understood part in the role of the translation of sugar in the animal economy."

In 1916, Schafer, in his "Endocrine Organs," writes as follows:

> "Foetuses in utero prevent glycosuria in the blood of the diabetic bitch; this with Hedon's experiment, the influence of

the blood of normal dogs and of depancreatized dogs, clearly indicates the influence of the pancreas upon carbohydrate metabolism due to a chemical agent circulating in the blood."

Schafer discusses Starling's definition of the hormone, his "chemical messenger," and himself proposes for the specific substance the general title "autocoid" substance or "autocoids"—self-medicinal agents or remedy; either exciting (hormone) or hormone-restraining—chalonic; considers the "nature of the pancreas autocoid provisional."

> "It would be convenient to refer to this hypothetical autocoid as insulin; it must, however, be considered that it is yet to be determined whether the active substance is present as such in the pancreas or exists there as pro-insulin which elsewhere becomes converted into an active autocoid."

He notes Zuelzer's observation of glycosuria prevented by pancreas extract; discusses "surgical removal" of the pancreas ducts in 1889 by von Mering and Minkowski, including ligature of the duct—the atrophied gland being implanted and the rest of the gland removed; diabetes did not occur. He considers all this "evidence of the internal secretion very complete."

Clinical experience, pathology, and histology have also contributed evidence of the dual role of the pancreas, the complete separate identity of its internal structure and mechanism. A recent exhaustive survey of this subject is found in a paper by Barron:[11]

> "In complete accord with the results obtained experimentally in animals, occlusion of the ducts by calculi in man does not result in diabetes mellitus unless there be actual injury to islets."

Work of Dr. Banting and Associates.

It was the reading of Barron's article by F. G. Banting in 1921 which led him, in association with C. H. Best, to undertake experiments with extracts of the degenerated gland upon the depancreatized dog with the object of utilizing extracts from the islet tissue free from proteolytic enzymes.

Then followed the use of the calf fetal pancreas extracts upon depancreatized dogs. Then, with the collaboration of their col-

[11] *Surgery, Gynecology and Obstetrics,* 1920, p. 447.

leagues, J. B. Collip, Department of Pathological Chemistry, W. R. Campbell and A. A. Fletcher, University of Toronto, Department of Medicine, and Toronto General Hospital, further experiments were undertaken with resort to extracts of the whole normal gland of other animals (ox, pig, etc.), alcohol being used as a means for the exclusion of the enzymes from the entire gland extract as prepared for injection.

It was found that active antidiabetic injections could be prepared from degenerated and from fetal glands, these already known to be free from enzymes. It was found that entire normal gland extracts when freed from enzymes gave similar results to the fetal and degenerated glands; they exhibited antidiabetic behavior, this proving that the exclusion of the enzymes (by chemical methods) yielded gland material of hormone properties. These injections, prepared from the degenerated gland, the fetal gland, and from the entire normal gland, by varying methods of extraction—aqueous, acid, alkaline, saline, neutral, and alcohol extracts from the entire normal gland in which alcohol was used for the exclusion of the enzymes—all exhibited antidiabetic action.

With the participation of Professor Macleod (in whose laboratory and under whose auspices it is well known that this work was begun) and Noble, Hepburn, Latchford, and others, the association of this "Toronto group," as it is commonly spoken of, was definitely undertaken, in order to engage co-ordinated personal participation in every field and in every detail—the experimental preparation of the gland extracts, and in the animal experimentation, the laboratory tests of the preparations—all this especially in connection with clinical application and study and obtaining of data in the observation of the physiological and clinical effects of the injections, with most complete laboratory check.

There was also enlisted co-operation in this clinical trying out of the pancreas extract in diabetes in hospitals and institutions and by physicians especially equipped for clinical observations in connection with complete laboratory data, etc.

In this connection a work of the utmost importance was also undertaken in the endeavor to ascertain if the action of pancreas extract upon the blood sugar of normal animals could be so controlled that it would afford a method by which to determine the potency of the extracts, and in developing the various modifications in the method of preparation.

In these experiments with rabbits it was also shown that convulsive reactions of the injection could be antidoted by injections of dextrose, this developing a prompt and dependable clinical recourse against any alarming symptoms (premonitory indications) by the oral administration of glucose and other sugars, fruit, etc.

The success of these investigations, in conjunction with the laboratory, in the testing of the preparations, has enormously facilitated the whole progress of the work.

Numerous have been the publications describing the methods of clinical use and the antidiabetic effects of the internal secretion principle extract.[12] A general survey of this whole subject, with special reference to the preparation, pharmacological assay, and laboratory investigations,[13] as well as other important contributions on this subject, have been made by Professor Macleod. The history of this research work, its development and its success, has been frequently referred to as a striking and unexampled achievement of team work.

The method of the preparation of the hormone extract, the principle of which is stated to be to circumvent the enzyme by alcohol, and which in all essential details is that used for the preparation of insulin, is described and more readily found by Banting, Best, Collip, Hepburn, Macleod, and Noble.[14] Briefly, this method as published is the alcohol extraction of the entire fresh gland (precipitation of the enzymes and proteins) and repeated alcohol extractions (including ether extraction) and alcohol precipitation. The final precipitate, taken up in aqueous solution suitable for injection, contains the active principle "with adherent, sticky, resinous substance." It has also been subsequently stated that further details for the purification of the injection, the solution of the hormone principle, have been withheld from publication. Great progress has been made with respect to the final purification and recovery of the active hormone free from this remnant of the proteinous constituents.

It is well known that hydrochloric acid has played an important

[12] Banting and Best, *J. Lab. Clin. Med.*, *7*, 251 (1922); Banting, Best, Collip, Campbell, Fletcher, *Can. Med. Assoc. J.*, *12*, 141 (1922); Banting and Best, *J. Lab. Clin. Med.*, *7*, 464 (1922); Banting, Best, Collip, Macleod, Noble, *Am. J. Physiol.*, *62* (1922).

[13] Macleod, *Brit. Med. J.*, 1922, p. 833.

[14] *Trans. Roy. Soc. Can.*, *16*, Sect. V, 1 (1922); abstracted in *C. A.*, *16*, 115 (1922).

part in the extraction and in the fractional precipitation of the hormone. The H-ion adjustment has been an essential factor in the isolation and precipitation of the hormone. Sulfuric acid has been proposed as a substitute for hydrochloric acid, and other precipitants in connection with the alcohol extraction are used.[15]

As a result of this collaboration and the interest of other laboratories and individual workers, the hormone extract has been greatly perfected and the insulin injection is a more potent and purified preparation than the original Toronto product.

Plans for Control and Standardization of Insulin.

It is well known that in the plan of the Toronto University it is proposed that patents for a method of preparation be sought, and for the purpose of control, only so far as certain formulated conditions are to be required of, and reciprocal relations undertaken by, those who should operate under these patents. The object, as stated, is to make the production of insulin (the specific hormone extract) of a wider general availability than might be probable under privately controlled patent; and also to forestall future patents.

Wide publicity has been given to this phase of the program of the Toronto University. It is highly desirable that the public should more clearly understand the subject of the patent in regard to the invention of medicinal substances, or new methods of the preparation thereof. The patent stimulates invention and thus other patents, and is as much in the interests of society as regards a therapeutic product as for some commonly used articles, device, or mechanism. In the field of science, in the first place, it constitutes a means of formal publication and claim, and presumes priority, and, if validity is maintained, establishes a priority of discovery which constitutes invention.

The adjudication of the patent is therefore a matter of great ethical and economic importance in applied chemistry, which, it may be said, is of great magnitude and importance industrially.

While this phase of the subject is of special interest and significance to makers of medicinal preparations, it is, however, quite secondary to that brilliantly conceived, considered scheme, too well known to particularize, with its purpose to establish therapeutic

[15] Doisy, Somogyi, and Shaffer, *J. Biol. Chem.*, *55*, xxxi (1923).

properties and method of use and at the same time to establish a certain standardization.

The intensity, persistence, and success with which this plan has been pursued is a familiar story—collaboration and co-operation to an extent and to an accomplishment hitherto unparalleled.

The inception of this plan, its adoption and pursuit, is due to the initiative and inspiration of Dr. Banting, and in consequence of his own conceived idea and his demonstration of the antidiabetic properties of even the earliest, crudest hormone extracts prepared in accordance with his theory and brought to a successful clinical trial.

Significance of Discovery of Insulin.

It was a fortunate thing that Dr. Banting—without preconceived opinions, having in his hands this history and summary of the evidence that the external secretion of the gland has no relation to the phenomena of clinical diabetes, that disease, even atrophy, of the acinic cells occurs without diabetes, but that diabetes does not appear without disease of the island of Langerhans—should have been led to see a possible clinical application and have pursued it to its brilliant issue, where others had approached, wavered, hesitated, or left off in the study of the hypothesis of the internal secretion hormone and its clinical application.

The possession of this hormone pancreas insulin extract means vastly more than this remedy for diabetes with all its great, immediate, assessed value. It has immensely stimulated and forwarded the study of diabetes in the course of the evolution of the chemistry of its preparation, method of use, and standardization; and the wide study and active research which it has inspired is shown in voluminous current literature dealing with every phase of the whole problem.

That this solution of the problem of the pancreas hormone in medicine should have come with such halting steps, should have so long escaped the decisive trial, which, as we have seen, would seem to have been inevitably suggested, may be accounted for by a state of mind which entertained no probability of the successful use of the pancreas extract in diabetes.

This state of mind goes back to the early belief that "pancreatin is destroyed in the stomach," so long insisted upon even after physiologists had shown that the pancreas enzymes, trypsin and lipase, were especially resistant to gastric juice and the evidence of their

insufficiency in the ailmentary tract, capable of laboratory demonstration, and likewise the ability to compensate this deficiency clinically by oral administration of the pancreas extract. Incidentally, the discovery of the normal participation of the pancreas juice in digestion within the stomach has given a definite status to the therapeutic use of pancreas extracts.

The failure to obtain definite reduction of blood sugar in true diabetes mellitus by pancreatins and such like pancreas extracts tended to create a skepticism toward the pursuit of pancreas therapy in diabetes. The failure of pancreas extract administration in diabetes is frequently commented upon in connection with Minkowski's experiment and its implication, but it is evident that these pancreas preparations, pancreatins, pancreas extracts, etc., were never designed to afford a means for obtaining conditions paralleling those experiments, and by nature were not competent to afford any conclusive test of the therapeutic possibilities suggested in the experiments of Minkowski.

As long ago as 1910, Biedl, in his work "Innere Secretion," makes the following comment on the theory of pancreatic diabetes:

> "All that can be said at present to be founded on reliable evidence is that normally an internal secretion is formed by the pancreas that plays a deciding role in the metabolism of the carbohydrates and whose absence is the sole cause of the deviations forming the diabetes.
>
> "The fact that only the fewest observers (Caparelli, Zuelzer, Dohrn and Mayer) saw any definite improvement following the ingestion of fresh or dried pancreas, while most of the leading men give statements to the contrary, is no proof against this assumption. It proves merely that the generally accepted methods of organo-therapy are not applicable in the treatment of diabetes. All the experience given by transplantation of the organ as well as by the establishment of 'parabiosis' (connecting the blood circulation of two animals) gives sufficient support to the said theory."

In striking confirmation of Biedl's critical comment, we see that the very first experiments "asking the question of Nature"—will a heterologous pancreas hormone extract, by parenteral administration, give antidiabetic action in experimental and in human diabetes? —were answered in the affirmative.

In that development of the plan which rested upon the essential feature of highly specialized clinical trial, individual and insti-

tutional, the difficulties and the hazards which beset the problem of establishing the therapeutic properties of insulin injection and usage become more and more evident, and with recognition of the wisdom of this plan. Whatever may be the method of manufacture which finally shall be perfected, and regardless of the matter of inventions in chemical methods, the product itself should be of a uniform standard everywhere, and as it has been worked out in consequence of the program of the Toronto University.

The method of preparation, standardization, is one which is widely available, and of a more practicable nature than at first appeared. This also is likely to be a matter of progress.

The widest participation of the manufacturing chemist is obviously desirable in order that the sources of supply shall be utilized to the best economical and technical advantage and with that highest possible attainment which is inevitable to be anticipated under such circumstances; and, lastly, that the preparation shall be correspondingly available in medicine.

COLOR AND CHEMICAL CONSTITUTION.*†

By V. E. Yarsley, B. Sc.

Concurrent with the increasing knowledge of the relative structure of chemical compounds came the desire to establish a relation between chemical constitution and physical properties. Color, the most striking characteristic of a compound, was among the first to receive attention. Many attempts have been made by different investigators to deduce a connection between chemical constitution and color.

The auxochrome chromophore theory of Otto Witt, put forward in 1876, was the first attempt in this direction. Witt suggested that two conditions were necessary to give a substance color and dyeing properties. (1) The presence of certain groupings of atoms to give a substance a potentiality for color; (2) it must also possess a salt-forming radical to bring out the color and dyeing properties. The necessary atomic groupings he termed the "chromophores," while the molecules containing them were the "chromo-

*A paper read before the Chemical Society of the University of Birmingham.

†Reprinted from *Chemical Age*.

gens." The auxiliary effect of certain groups was usually necessary for the production of color, these groups Witt termed the "auxochromes." Thus for the development of dyes, auxochromes are necessary, although they are not essential for color production. This theory was very useful, in that it successfully generalized what might have been merely a disjointed collection of facts.

In 1888 H. E. Armstrong put forward his famous "quinonoid theory," which attributed color production to the presence of a quinonoid grouping in the molecule. Although it has been shown that many colored compounds contain the linking, there are many compounds, *e. g.*, primulene, which cannot be arranged so as to contain a quinonoid structure. Subsequent investigators modified the original theory, but these were no more successful than the original.

Observing that the fulvenes, which do not contain the quinonoid structure, are colored, H. von Leibig suggested that the essential arrangement for color production is that contained both by the fulvenes and quinonoid compounds, *viz.*, -Ä-Ä-Ä-. This theory successfully explains many curious cases of color production, but fails to show why such compounds as naphthalene, diphenyl and nitrobenzene, which undoubtedly contain Leibig's essential chromophore, are colorless.

Kauffmann, who examined these substances under the influence of the Tesla rays, postulated that the usual Kekulé arrangement of bonds in the case of these substances is incorrect. Introduction of certain groups, *e. g.*, OH into nitrobenzene, causes immediate rearrangement, with the result that the bonds take up the Kekulé arrangement, and color results.

This brief consideration of earlier theories shows that speculation based on visible color alone was unsatisfactory. Although as early as 1879 Hartley had shown that there was a definite connection between constitution and absorption it was not until the early years of the present century that investigators showed any confidence in the theory which he put forward. The failure of early work had served to show that a deeper cause must be sought. The gradual revision of ideas is reflected in the following quotation: "It is now generally recognized that a more precise meaning must be given to the idea of color than has hitherto been the case. The production of physiological color, due to the occurrence of absorption in the visible spectrum, is more or less an accidental circum-

stance. Absorption bands may occur in the ultra violet of equal importance with those in the visible spectrum. In some cases a change in the frequency of the absorbed ray may cause a band to move from the ultra violet to the visible region, without any change in form. A colorless substance may thus be converted to a colored one without any real change in constitution having taken place, the alteration in the molecule only being of such nature as to cause a certain retardation of those oscillations within it which give rise to the absorption. A study of the color of a substance thus involves the examination of its entire visible and ultra violet spectrum, and, as Hartley and his successors have shown, of the change of absorption with the concentration of the absorbing substance." (*Chem. Soc. Ann. Rep.*, 1907.)

Hartley's method of recording absorption spectra is that in general use. The positions of the bands for varying thickness of solution are plotted with wavelengths as abscissæ and thickness of solution as ordinate. A later modification, due to Hartley himself, was to plot frequency with log of thickness. The practical difficulties experienced in detecting the somewhat elusive edge of the band, are eradicated by the use of the spectrophotometer. In this case curves are obtained connecting percentage of light absorbed with frequency.

Many theories have been advanced on the nature of the vibrations causing the absorption bands. Baly and Desch suggested that it was due to dynamic isomerism, whereby a substance underwent tautomeric change from the ketonic to the enolic form. Later, in conjunction with Stewart, Baly pointed out that in cases where true tautomerism was impossible, it was nevertheless possible to imagine a vibration between two forms in which the valencies were differently arranged. Such a molecular rearrangement not involving the migration of a hydrogen atom, they termed "Isorrepesis," and they suggested that this type of dynamic isomerism was responsible for the production of bands. Baly suggested that the residual affinities between the atoms in the molecule unlocked the rigid structure and made possible the isorrepesis within the molecule. On the basis of this theory, color change in the case of the nitranilines and nitrophenols is readily explained.

The theory gives very little greater generalization than the older one, but it is notable in that it recognizes that not mere orien-

tation, but an internal vibration between the goups in the molecule is the cause of color.

In that branch of the subject dealing with depth of color much progress has been made. Nietzki showed that in general the color of a dyestuff was deepened by adding groups so as to increase its molecular weight, the deepening effect being more or less proportional to the weight of the groups added. This generalization, known as "Nietzki's Rule," was not based on any systematic investigation and many exceptions have been noted. Schutze pointed out that the effect of an added atom or group depends not on its weight alone, but also on its chemical nature and on its position in the molecule.

It was found that some groups produced a deepening of color, whilst some had a contrary effect. The former were termed "bathochromic," the latter "hypsochromic."

The auxochromic effect of the NH_2 and OH groups is illustrated in the dyes of the triphenylmethane series; the change in color with increase in molecular weight being very definite. Other useful series are the alizarine dyes, the color in this instance varying with constitution, and also with the mordant used. The variation in the latter case has been shown to be due, not to differences in weight, but to difference in the electropositivity of the metallic radical, the color being deeper the more positive the metal.

Hewitt suggested that the chief oscillation frequency is less, and consequently the color deeper, the longer the chain of alternate double linkages in the molecule. Watson, in 1914, pointed out that Hewitt's rule must be further qualified in order that it may be generally applicable. He suggested that the conjugated chain required definition, as otherwise, such substances as naphthalene with a fairly long conjugated chain would be expected to exhibit color. A further qualification suggested later was that the conjugated chain must be contained in a quinonoid formula.

Thus, we might restate Hewitt's rule "that the chief oscillation frequency is less, and consequently the color deeper, the longer the conjugated chain contained in the quinonoid formula in the substance." No connection has yet been obtained between the length and nature of the chain, and the wavelength of the light absorbed, although both on theoretical and practical grounds such a relationship is highly probable.

Of specific groups of substances those known as indicators are

of fundamental importance. The efficiency of an indicator depends on the rapidity of the color change on the addition of acid or alkali. The cause of these changes is of great theoretical interest and practical importance, but it still lurks in obscurity.

Ostwald's ideas held the field for rather more than ten years and it was not until 1903 that they were successfully challenged. For the sake of simplicity attention will be confined to phenolphthalein, since this substance played the greatest part in the course of the discussion.

Steiglitz pointed out that it was highly improbable that phenolphthalein, whose molecule contains no chromophoric group, should become red merely by ionization. From this time ionization was no longer accepted as being the root cause of indicator color, the possibility of intramolecular rearrangement in the molecule being a much more plausible explanation. The insufficiency of the ionic hypothesis is shown by the series of color changes observed with phenolphthalein in passing from the mono to the tri sodium salt, and thence again to red mono salt.

Hentzch, upon whose pseudo acid researches the modern chemical theory of indicators depends, showed conclusively that the production of colored from colorless substances necessitate a change in structure and is independent of ionic action.

Thus we may say that the color change in an indicator is due to the influence of an electropositive metal causing structural changes, and the formation of a quinonoid grouping. As a secondary process we get the formation of ions, and these are colored not on account of ionization alone, but because they are produced by a colored salt.

Another group of substances inviting special attention is that which includes fluorescent bodies. Much experimental work has been done and many theories put forward on the relation between fluorescence and constitution. Hewitt suggested that it was due to a special type of tautomerism, called by him "double symmetrical fluorescence." This theory is illustrated in the symmetrical vibration possible in anthracene and fluorescein.

Kauffmann extended his examination of substances in the Tesla rays to those exhibiting fluorescence, but although much was observed very little generalization was possible. The work is being carried forward by McVicker, Marsh, and Stewart, but their investigations are not yet complete.

Thus, in spite of the enormous amount of experimental work

which has been done, there does not exist any real relationship between color and constitution. It is highly probable that the final theory of selective adsorption will be the one which takes full account of color as an essentially dynamic property, the molecule being regarded not as a rigid structure, but one capable of rapid oscillations. Working on these lines it may become possible to recognize in a general way the characteristic vibrations associated with specific groups of atoms, and hence to predict color. (The author is indebted to the standard work of Professor H. E. Watson.)

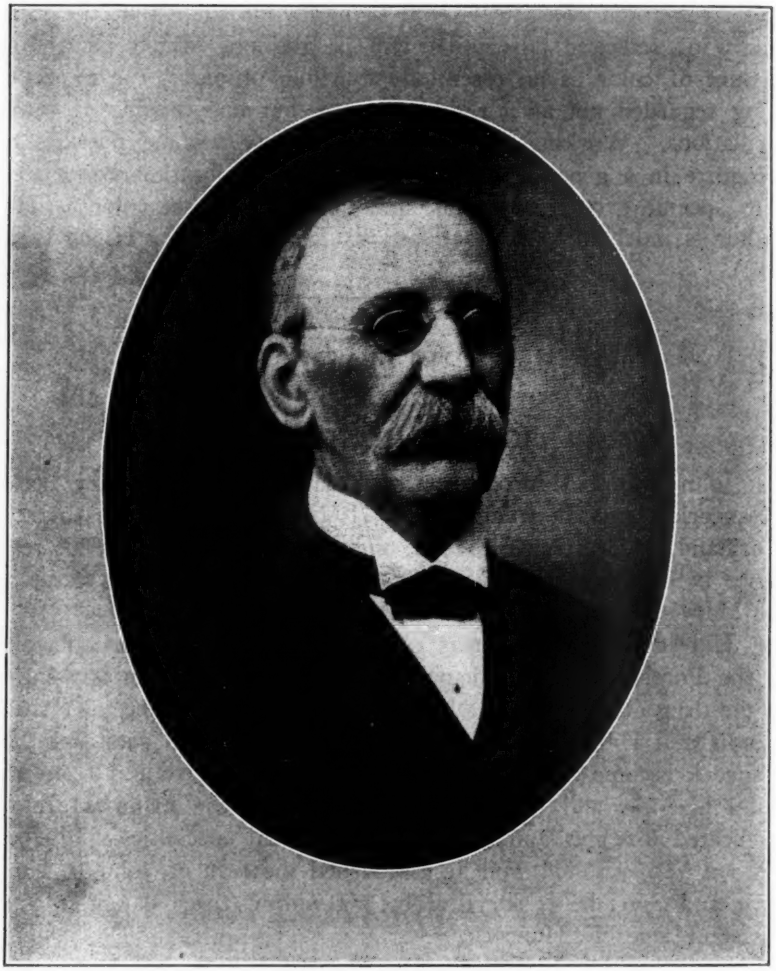
OBITUARY

JOHN F. HANCOCK.

John Francis Hancock, son of John Hancock and Mary Leeke (Hancock), was born at Forest House, Anne Arundel County, Maryland, on September 9, 1834, and died of pneumonia at his residence in Baltimore on November 12, 1923. His forbears came to St. Mary's, the first settlement in Maryland, in 1664.

His early education was obtained in the district schools and at the Forest House Academy. In 1855 he became an apprentice in the drug store of Dr. J. L. Large, of Baltimore; one year later, Landis and Hancock succeeded to the business, and soon John F. Hancock became the sole proprietor. In 1899 he retired from the retail business and with his two sons began the manufacture of medicated lozenges and other pharmaceutical specialties. In 1903 his son William died, and he established the firm of John F. Hancock and Son; he is survived by his widow, three daughters and his son, James E. Hancock.

Graduating from the Maryland College of Pharmacy in 1860, he soon became a member of the College, and later was made a member of the Board of Examiners, and president of the Maryland College of Pharmacy in 1872-74. He was awarded the honorary degree of Master of Pharmacy in 1871 by his alma mater, and had conferred upon him the honorary degree of Doctor of Pharmacy by the University of Maryland in 1907. He was given the honorary degree of Master in Pharmacy by the Philadelphia College of Pharmacy in 1908.



JOHN F. HANCOCK.

He has held many positions of honor and trust, both within and without his profession. He was elected lecturer in pharmacy at the Baltimore College of Physicians and Surgeons in 1885, and served as a member of the Maryland Board of Pharmacy for twelve years. He was president of the Maryland Pharmaceutical Association. He was an honorary member of the Pennsylvania Pharmaceutical Association, of the New Jersey Pharmaceutical Association

and of the New Hampshire Pharmaceutical Association, and an active member of the Southern Maryland Society, and of the Sons of the American Revolution. He was a member for a time of the School Board for Baltimore City and of the Board of Directors of the Baltimore Eastern Dispensary, and of the Board of Trustees of St. Mary's Industrial School. He was also the vice-president of the Free Summer Excursion Society of Baltimore.

He was a devoted member of the American Pharmaceutical Association for sixty years, and its one-time (1873-74) president. While recognizing the necessity of commercial pharmacy in pharmaceutical practice, he was deeply interested in promoting professional pharmacy and worked untiringly toward this end. He fathered the movement of the association to establish a memorial to his friend, the late William Procter, Jr., the "Father of American Pharmacy," was made chairman of the committee on the William Procter, Jr., Memorial Fund, and labored with untiring zeal for more than a score of years for the accumulation of the present trust fund, now amounting to about $11,000.

John F. Hancock was a man of unusual character and charming personality. As the writer has written of him elsewhere (*Journal, A. Ph. A.*, December, 1923):

"The activating motive of his life was honesty—honesty to himself and to his fellowman. He confided in his friends and never betrayed a confidence placed in him, no matter what advantage he might secure thereby. While he never pressed his views unduly, he was firm for the right as he saw the right, even though he stood alone. He flattered nobody, he persecuted nobody, he belittled nobody, but was always frank and open. He was ever the courteous, kindly, tolerant, Christian gentleman and never the politician. He gave everybody his due, was true to his friends, generous to his adversaries; enemies he had none. The dominant notes of his personality were kindness and service; he lived for others. Like Abou Ben Adhem, he loved his fellowmen more than he loved himself, and the memory of his being will stay with us through the years to come to stimulate and inspire, and through us, others. Just as the ripples on the water from a stone cast upon its surface may widen and extend on and on to infinity, so may the influence of a life like John F. Hancock live long after he has passed."

J. W. England.

SCIENTIFIC AND TECHNICAL ABSTRACTS

Silica Glass.—Among the many products made available by the perfection of the electric furnace, scarcely any are so peculiar in properties and serviceable in certain directions as the glass made from pure silica. Silicates in the form of transparent masses have been familiar for many centuries, but the direct melting of silica itself was not commercially possible until electric current became available at reasonable rates. Advance sheets of the report on the mineral resources of the United States for 1922 give, among other data, considerable information as to the silica-glass industry in this country. The text was prepared by F. J. Katz, and is issued by the U. S. Geological Survey as pamphlet II.21, "Silica in 1922," much of the manufacturing detail being furnished by F. L. Hess.

Two important differences are noted between common glass and silica glass. The latter bears sudden, extreme changes of temperature and transmits a large proportion of ultra-violet radiation. Vessels of silica glass can be dipped when red-hot into cold water without cracking. On comparing two sheets, one of common glass and the other of quartz glass, both quite transparent to the eye, it will be found that the common glass is as opaque to ultra-violet light as a piece of cardboard. The same relative opacity is noted with mica, celluloid, gelatin and many other transparent materials.

In the practical production of silica glass (generally termed "quartz glass") two grades are familiar: transparent and translucent. The latter may be almost opaque to ordinary light. The opacity is usually due to gas bubbles. In the manufacture of this form a good grade of quartz sand is satisfactory, but for the transparent form a carefully selected and pure material in large pieces must be used. High-grade Brazilian pebble is generally used. The cost of the product is seriously enhanced by the fact that at the temperature of fusion considerable loss from volatilization occurs. It is stated that five pounds of quartz can be fused in twenty minutes in the electric furnace, but about one-fifth of the material will be lost in that time. This is not of very great moment in the cheaper grades, but dealing with high-class quartz, the loss is of great significance.

The first quartz glass articles were all hand-made, and this method is still followed in making crucibles, beakers and similar ware. Tubing and rods are now made by machinery. At the laboratory of the General Electric Company at Lynn, Mass., under supervision of Dr. E. R. Berry, who has been seven years experimenting in this line, an extremely clear glass is made. Rods and tubes twenty-six feet long have been made. Much difficulty has been experienced in getting skilled men for this work. When quartz is at the melting point the light is dazzling, dark goggles must be used and a dark glass plate also interposed. Little of that part of the mass which is not incandescent can be seen, the heat must be interrupted from time to time, and the article allowed to cool in order that the progress of the work may be examined. In making tubes for quartz mercury-arc lamps, now so extensively used, it is necessary that the quartz be welded with a glass that can be worked at a lower temperature. This is accomplished by a mixture of quartz and pyrex glass graded so that the proportions change from pure quartz to pure pyrex. Quartz tubing several inches in diameter and in complex coils is now made for industrial uses. The high index of refraction and transparency to ultra-violet radiation are two qualities which will be of great value in astronomy and microscopy and Dr. Berry hopes to obtain blocks suitable for telescope lenses. Quartz mercury-arc lamps are used in sterilizing water in the tanks in public bathhouses. It is stated that excellent results have been obtained by this method. Application has also been made of the curative effect of ultra-violet rays. The writer of this note knows of a case in which a rather obstinate dry tetter has yielded quite markedly to a few seconds occasional exposure to ultra-violet light.

In the analytic laboratory quartz dishes and crucibles have been useful as a substitute for platinum, but, unfortunately, they are unavailable in some operations, and the analyst has still to bear the burden that the fashionable use of platinum imposes.

H. L.

Air Pollution by Automobile Exhausts.—Ample evidence exists as to the dangerous nature of the exhaust gases from internal combustion engines. These differ considerably in composition, depending on the composition of the mixture of air and combustible that may be fed to the cylinders. Imperfect combustion often occurs,

by which carbon monoxide, an extremely poisonous gas, is formed. Drs. Henderson and Haggard, of New Haven, Conn., have made and published extensive investigations into the amounts of carbon monoxide in air pollution by automobile exhausts. Their results appeared in the *Journal of the American Medical Association* (1923, 31, 385), unde the title, "Health Hazards from Automobile Exhaust Gases in City Streets, Garages and Repair Shops." In the open country, with the limited number of operating autos, pollution is not likely to be serious, but in narrow, congested city streets, and in overcrowded garages, the concentration of the products of imperfect combustion of the motor liquids is apt to be marked. Most autos discharge their exhausts horizontally about the level of the car axles, so that the air on the level of the occupants of the following car is sure to be polluted. The investigators made many tests and found that this method of discharge is decidedly objectionable. They recommend a vertical exhaust by means of a pipe directed so as to cause the exhaust to be mixed with air above the respiratory zone of the passengers. Such a modification in auto construction will, probably, not be brought about except by legislation. Henderson and Haggard suggest that the simplest and most efficient method would be taxation. If a license fee of say $25, in addition to the regular fee was levied on all cars not provided with vertical exhaust, the condition would be promptly remedied.

The amount of visible smoke is not an index of the carbon monoxide content of the gases discharged. Chemical tests showed that the air of garages and repair shops is, as a rule, quite insanitary. Many mechanics and drivers suffer frequently from headache and other objectionable conditions due to partial asphyxiation. Fatal accidents in garages are frequently reported. The ordinary horizontal exhaust mixes poisonous gases in the air of city streets to a depth of about ten feet. It dissipates the heat of the gas and prevents it rising and passing away. The vertical exhaust is far better.

H. L.

Dangers Incident to the Use of Carbon Tetrachloride Fire Extinguishers.—Jacques Fohlen, writing in a recent issue of *Technique Moderne,* notes the influence of moisture upon the toxicity of decomposing carbon tetrachloride. He states that phosgene ($COCl_2$) is formed by heating carbon tetrachloride at temperatures

from 200 degrees C. to 800 degrees C. In dry air heat reacts with carbon tetrachloride according to the equation $2CCl_4+O_2=2COCl_2+2Cl_2$, but the yield is very small, the maximum being 0.4 of 1 per cent., although the theoretical yield is 64 per cent.

In the presence of combustible organic matter the following reaction takes place with a maximum yield of 0.75 of 1 per cent. The yield is theoretically 128 per cent.:

$$2C+O_2+2Cl_2=2COCl_2.$$

In the presence of moist air the following reaction takes place with a maximum yield of 64 per cent.:

$$CCl_2+H_2O=COCl_2+2HCl.$$

Fire extinguishers containing carbon tetrachloride should only be used in well-ventilated compartments; they should not be used in the presence of moist air; and it is very important to note that after their use water should not be sprayed on objects to cool them off.

NEWS ITEMS AND PERSONAL NOTES

Prominent Philadelphia Professional Men, Educators, Etc., Give Talks at Assembly Periods of Philadelphia College of Pharmacy and Science.—Last year two assembly periods were arranged in the roster, one for the juniors and one for the seniors. These assemblies were so successful that they have been repeated this year. At these periods the entire class gathers for a musical service, a debate, or an inspirational talk upon some subject not directly connected with the college work, but making for higher ideals of citizenship and responsibility.

The list of speakers who have either appeared upon the program thus far this year or have accepted invitations to address the classes and are scheduled to appear later in the College year is notable for the prominence of many of those whose names appear.

It is as follows:

Dr. Edgar F. Smith, Dr. Russell Conwell, Hon. Horace Stern, Hon. Franklin Spencer Edmonds, Hon. John Weaver, Hon. J. M.

Patterson, Col. S. P. Wetherill, Jr., Dr. McCartney, Dr. A. C. James, Dr. Robert Norwood, Dr. E. Heyl Delk, Dr. A. Pohlman, Dr. Percy Stockman, Dr. Ernest Bawden, Dr. Thomas Nitingale, of London, and Dr. Charles E. Jefferson, of New York.

The College orchestra or Glee Club usually furnish music and community singing of patriotic or college songs is a regular feature of the program.

The "Wellcome" Photographic Exposure Calculator, Handbook and Diary, 1924.—A glance at this friendly counsellor of photographers indicates that since the last editon, there has been considerable revision and many additions to the list of plates and films, which is the most complete we know both in regard to exposure speed and development speed. Here and there we find slight increases in sensitiveness to light (exposure speed) sometimes associated with diminished contrast-giving power (development speed) necessitating, increased time of development, a much more important point in most instances.

The most notable change, however, is in the number of films, particularly roll films, which have been introduced and details of which appear in these pages.

The calculator itself appears to have reached perfection for a single scale instrument, but we note a simplification of the monthly light tables which now consist of four columns of light conditions instead of five, each condition demanding double the exposure of that preceding it. The latitude of modern plates and films is ample to justify this simplification and as it is accompanied by higher ratings for the poorer lights, it is a further advantage because it affords a protection against the greatest danger in photography, namely, underexposure.

In the diary and memorandum section it is to be noted that by an ingenious arrangement of the memoranda pages, the photographer is able to employ twenty-four of these pages either for additional exposure records or for miscellaneous notes as he may prefer.

As an example of the nicety which Burroughs, Wellcome & Co. devote to all their productions, publications and products alike, we note that the decorations throughout the book have, this year, been changed from Egyptian to Indian in character in order to

harmonize with the frontispiece illustrations, one of which depicts an incident of the Prince of Wales' tour in India and the other is one of the Mount Everest Expedition photographs. Both were taken by the official photographers, both were developed with "Tabloid" "Rytol" and both are excellent evidence that fine photography is the outcome of the methods and materials recommended in this valuable little book.

Metric Standards Bill Introduced in Congress.—Among the first bills introduced in the new session of Congress are the Metric Standards Bills, providing for gradual adoption of the metric units of weights and measures in merchandising.

The metric bill was introduced in the House of Representatives by Hon. Fred A. Britten, of Illinois, and in the Senate by Hon. Edwin F. Ladd, of North Dakota. The Legislatures of these States, in company with many others, have petitioned Congress to enact metric standards laws. More than 100,000 petitions, directly representing several millions of voters, are pending before Congress, urging favorable action on adoption of the world units for weighing and measuring.

The simple decimal nature of the metric system is ingeniously stressed in the numbers of the metric bills themselves—Congressman Britten's being number 10 in the House and Senator Ladd's bill number 100 in the Senate.

According to the provisions of the Britten-Ladd bill, the buying and selling of goods, wares and merchandise will be in terms of the metric units after a period of ten years. Manufacturers are to use whatever measures they choose in production, the bill providing "That nothing in this act shall be understood or construed as applying to the construction or use in the arts, manufacture or industry of any specification or drawing, tool, machine, or other appliance or implement designed, constructed or graduated in any desired system." This safeguards manufacturing interests. Hundreds of great industrial concerns are urging the metric legislation on this basis.

Rules and regulations for the enforcement of the metric act are to be made and promulgated by the United States Secretary of Commerce.

American Products in Far East.—A report of the meetings and reviews of the proceedings has been received covering the Fifth Congress of the Far Eastern Association of Tropical Medicine, held in Singapore, September 3 to 17, 1923.

It was attended by delegates and representatives from the Straits Settlements, the Federated Malay States, Australia, Borneo, Ceylon, India, China, Japan, Dutch East Indies, Philippine Islands, Siam and others.

Incidentally, H. K. Mulford Company, Philadelphia, are to be congratulated upon the fact that the report includes special mention of the display of Mulford Biological Products, and of the artistic arrangement of their exhibit.

BOOK REVIEWS

Medikamentenlehre fur Krankenpfleger und Krankenschwester. By Dr. Paul Fleissig. Fifth enlarged and revised edition. 18 mo., xvi—197 pages. Urban & Schwarzenberg. Berlin and Vienna.

This is a neat and compact account of the sources, properties and uses of all the medicines commonly used in hospital practice. In his introduction, the author expresses the view that hospital stewards and nurses should know something about the drugs they use. It is, as he admits, an open question whether the necessarily incomplete knowledge thus acquired by the hospital attendants may not be more of a danger than an advantage. Unquestionably, no one would hold that only the medical attendants should have any knowledge about medicines, their uses and effects, yet it is difficult to draw the line. There is a danger that the "little learning" may be overestimated and the doctor's orders be modified.

So far as the present work is concerned, the information is extensive, accurate and well set forth. The fact that work has gone through five editions in eight years, including the years of the war, during which no edition was issued, is evidence of its value. It is very neatly printed on good paper and of convenient size. A good deal of space is devoted to questions of discipline and management, so that it serves as a manual of conduct as well as a guide to mat-

teria medica and pharmacology. To the English-speaking physician and chemist familiar with the language the work is valuable because it gives much information as to the names of familiar chemical substances which, owing to the peculiarities of the German language, may mislead and cause erroneous translations. Thus attention is called to the difference between "Bleiessig" and "essigsaures Blei." The former is lead subacetate, the latter lead acetate. Attention is also called to the fatal results that have followed confusing "Baryum sulfuratum" with "Baryum sulfuricum." The former is barium sulphide, a poisonous compound, the latter, barium sulphate, practically inert. It seems that the danger could be avoided by designating officially the sulphide as "Baryum sulphidum." This might not be good German or good Latin, but practical questions of safety should control in such cases. Much information is given concerning the preparation of mixtures for external and internal use and many pharmacy operations. For all who read the language, the book will be of much service.

HENRY LEFFMANN.

DENTAL FORMULARY. By Hermann Prinz, A. M., D. D. S., M. D., Evans Dental Institute, University of Pennsylvania. Third edition, 328 pp. $3.50. Lea and Febiger, Philadelphia and New York.

As the author of this book states, it has been prepared to furnish the busy practitioner and the student, a reliable guide for technical information and special methods of procedure. It does this very well and in a satisfactory and comprehensive manner, giving formulas for all types of dental products, as Plaster-of-Paris preparations, moulding materials, waxes, impression compounds, cements, adhesives, varnishes, alloys, amalgams, preparations for the mouth and teeth, and many other type formulas that would be of particular value to the dentist.

A comprehensive chapter on "Pharmaceutical Compounds" is given, covering solutions of various types, pastes and powders, used in a dentist's daily practice.

Another chapter gives an index to oral diseases—their etiology, diagnosis and treatment, immediate treatment of acute poisoning, saliva and urine analysis, diagnostic hints.

A final chapter called "Miscellaneous," seems a bit out of place

as far as a "Dental" formulary is concerned, although the author states that many of the formulas and preparations listed, represent actual inquiries which he has received from time to time. For the pharmacist, this chapter alone would be quite valuable but just how would a dentist use formulas for hair tonics, shampoos, dyes and depilatories, skin creams and lotions, nail bleaches, shaving cream, foot powders, corn remedies, embalming fluids, writing inks, anti-freeze compounds, straw hat cleaners? We cannot help but feel that formulas of this type take for more than the "busy practitioner" (for whom the book is prepared).

The author has not limited his work to a single type formula on a subjcet, but has listed anywhere from two or three to a dozen formulas. The formulas given are not "personal pets," but represent those of proven value collected from many sources. Special methods of manipulation are given here and there which would be particularly welcome on many occasions.

While the book is prepared primarily for dentist's use, for which there is no question as to its value, it will undoubtedly also be of value to many pharmacists, particularly to those who are in touch with, and aid the dentists of their communities in supplying proper materials and preparations for their office use.

For the pharmacists' own use, the chapter on tooth and mouth preparations, with formulas for washes, powders, soaps and pastes, and the chapter on miscellaneous formulas, would be very useful.

A. B. N.

Chemistry—Inorganic and Organic. By Charles Loudon Bloxam. Revised by Arthur G. Bloxam and S. Judd Lewis. With 310 illutrations. Published by P. Blakiston's Son & Co., Philadelphia. Price, $9.

The edition now before us, dated 1923, is the eleventh, the first having appeared in 1853, when chemistry, as we now know it, was in its infancy.

Bloxam's Chemistry, in its 775 pages, presents the philosophic aspects of the science, and deals descriptively with a large number of inorganic and of organic chemicals. Indeed, it gives space also to some of the more important industries in which chemistry plays a part. Naturally the extent of the field covered—theoretical, descriptive and industrial, both inorganic and organic—has made

necessary brevity of treatment, and abruptness of transition from one subject to another, which makes the book unsatisfactory for beginners. The advanced student can, however, study this volume with profit; and the seasoned chemist will find in its pages much information not usually included in a single volume.

The first part, comprising 278 pages, is devoted to a consideration of the non-metallic elements. The next division, of 70 pages, has to do with physical chemistry, including the gas laws, electrochemistry, the chemistry of colloids, crystallography, the phase rule, mass action, dissociation, spectroscopy, radio-activity, and related subjects. The third part deals with the chemistry of the metals; and the fourth part of 260 pages is devoted to organic chemistry.

The book includes a wealth of material, is up-to-date, reliable, and is well-written. It is a book well worth having.

J. W. S.

GOVERNMENT BULLETINS.

A new historic map of the United States. "Know America First" is a popular slogan, and a Government publication is just announced which has value in the application of it. This is entitled, "Boundaries, Areas, Geographic Centers, and Altitudes of the United States and of the Several States, With a Brief Record of Important Changes in Their Territory," by E. M. Douglas, and has been isued by the Department of the Interior as Bulletin 689 of the Geological Survey. The report is sold by the Superintendent of Documents, Washington, D. C., at nominal cost. It gives numerous little-known facts relating to the organization of the original thirteen colonies and of the States after the Revolution.

California has within its boundaries the highest and the lowest points of dry land in the United States proper, and Alaska has the highest mountain peak in the possession of the United States. Colorado is the State having the greatest average altitude; Delaware has the least.

The bulletin contains a facsimile reproduction of a map of the British and French possessions in America as they were known in 1755. A copy of that map was used in the preparation of the treaty with Great Britain in 1782, when the United States was first recognized as an independent nation. The book also contains nu-

merous other maps illustrating the growth of the United States and the changes in its boundaries from early colonial days up to the present time.

The statement in the official announcement above that the United States was recognized as an independent nation by the treaty of 1782, is not quite accurate. That treaty recognized the thirteen states by name as independent sovereignties. The term "United States" had been officially adopted by the Continental Congress in August, 1776, as a designation, but state sovereignty was the dominant note for many years thereafter.—H. L.